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ORIGINAL RESEARCH

A Bibliometric Study of Interleukin Cytokines in the Treatment of Intervertebral Disc Degeneration

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Background: In recent years, the research on the occurrence and development of interleukin in intervertebral disc degeneration has been more and more extensive. The purpose of this study is to predict the future research direction or prospect by analyzing the relevant literature in this field.

Objective: Interleukin family cytokines are becoming more and more important in the research field of intervertebral disc degeneration, but all previous studies only focus on one aspect and are not comprehensive. We revealed the most influential countries and institutions in the field of interleukin, cytokine and intervertebral disc therapy. Systematic analysis of interleukin family cytokines and intervertebral disc degeneration and summary of related mechanisms will help to further promote the progress of related clinical treatment.

Methods: The related articles published in 1 January 2015–1 December 2024 were all from network science (WOS), and charts were made and analyzed by using social science statistics software package and GraphPad Prism 8 software. Using VOS viewer software and CiteSpace software, the research trend of keywords is analyzed visually.

Results: China has made the most significant contribution in this field. In addition, the research papers on IL-1 cytokines and intervertebral disc degeneration are the most, and Huazhong University of Science and Technology has published the most papers. Spine is the magazine that publishes the largest number of related documents. Preclinical medicine, especially immunology, plays a key role in this field. In hot spots, the focus of research can be divided into two parts (intervertebral disc degeneration and nucleus pulposus cells; The expression of interleukin and cytokine).

Conclusion: This marks the first bibliometric analysis in this field and provides a comprehensive literature overview. Our findings clarify the future research direction and various cooperative relationships. Targeted therapy for interleukin and cytokine may be an important development trend in the future.

Keywords: intervertebral disc degeneration, interleukin, cytokine, bibliometrics, targeted therapeutic

Introduction

Intervertebral disc degeneration is the main pathogenic factor of low back pain, which seriously affects the health of elderly patients and also brings great burden to society and family.[1] Generally speaking, from adulthood, intervertebral discs begin to degenerate under the influence of age, biomechanics, biochemistry and autoimmune inflammatory response. Intervertebral disc degeneration is a gradual pathological process, which begins with the change of the microenvironment of intervertebral disc cells and eventually develops into the change of intervertebral disc structure and function.[2,3] The main pathological characteristics of intervertebral disc degeneration are the activation and release of inflammatory cytokines.[4,5] At present, there are more than 100 kinds of cytokines known, and there are dozens of cytokines involved in the process of intervertebral disc degeneration. For example, the release of interleukin (ILs) may lead to the increase of the expression of catabolic enzymes and the degradation of extracellular matrix, which may lead to the apoptosis of intervertebral disc cells and eventually lead to the degeneration of intervertebral disc.[5] More than 10 members of the interleukin family have been proved to be related to this

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field, so it can be considered that the interleukin family cytokines are an important cytokine group involved in the process of intervertebral disc degeneration. With its further expansion in the research field of intervertebral disc degeneration, it is very important to determine its related trends and research hotspots.

Bibliometrics is a practical analysis method, which can quantitatively and qualitatively evaluate the long-term trend of research activities, and it depends on the indicators of literature database. It provides a convenient way to understand the development trend in a specific research field, and it is also convenient for scholars to understand the ranking of academic groups or researchers. Moreover, bibliometrics also provides supporting evidence, which is helpful for researchers to make strategies or decisions.[6,7] According to previous literature reports, bibliometrics research methods have been widely used in the study of the endocrine system,[8,9] cardiovascular system,[10,11] digestive system and respiratory system diseases,[12–15] as well as orthopedic system,[16,17] but the research field of interleukin family cytokines and intervertebral disc degeneration is quite rare. Peng et al's research has pointed out that inflammatory reaction is the main pathogenesis of intervertebral disc degeneration, and inflammatory reaction produces a large number of cytokines, which plays an important role in the process of intervertebral disc degeneration.[4] The interleukin family is recognized as the most important cytokine family, including 38 members, among which IL-1 and IL-6 have long been considered as two most important cytokines involved in the process of intervertebral disc degeneration.[18–21] Other members such as IL-2, IL-9 and IL-33 may also be inextricably linked with intervertebral disc degeneration, some of which may promote the development of the disease, while others may have a certain inhibitory effect on the progress of the disease.[22–24] They provide new opportunities for the treatment and prevention of intervertebral disc degeneration, and may be one of the main measures for the treatment of this disease in the future.

In recent years, many articles have emphasized the application strategy or future prospect of interleukin family cytokines in the treatment of intervertebral disc degeneration diseases. However, most researchers only explore from a single direction, which may lead to the narrowness of the research results. Moreover, the related literature summarizes different keywords, and a large number of keywords make it difficult for subsequent researchers to accurately locate information in PubMed, Web Science (WOS) or other databases. Therefore, it is very necessary to comprehensively analyze the current situation of this research and reveal the current or future hot spots from multiple angles. We use bibliometric analysis to reveal the global research trend, evaluate the related research results of interleukin family cytokines involved in intervertebral disc degeneration diseases, and predict the possible hot spots in the future. As we expected, the data extracted from this analysis can show the most important research content of interleukin family cytokines in this field, aiming at further analyzing its clinical value for intervertebral disc degeneration diseases and providing reference for future development.

Materials and Methods

Data Source and Search Strategy

The study included studies published from 1 January 2015–1 December 2024. Scholars used to think that SCIE, the online database of Web Science (WOS), is one of the most suitable tools for collecting data, so all the publications needed in this study were obtained from this database. At the same time, in order to avoid the error caused by the periodic update of the database, our team completed the search within one day on December 21, 2024 to avoid the error of data update (just copy and paste). The search strategy was as follows: Topic Sentence (TS) =(interleukin and lumbar disc degeneration)) OR TS=(interleukin and Degenerative Disc Disease)) OR TS=(interleukin and spine disc degenerative)) OR TS=(interleukin and degeneration of the intervertebral)) OR TS=(IL and lumbar disc degeneration)) OR TS=(IL and Degenerative Disc Disease)) OR TS=(IL and spine disc degenerative)) OR TS=(IL and degeneration of the intervertebral). This study only contained original articles and comments with standard peer review. Original articles and reviews were reviewed by other experts and scholars in the same field, and we also excluded other types of research and repeated articles. This process was completed by two different authors of this study, and if there was a big disagreement, it was finally decided by the experienced correspondent. The research selection process is shown in Figure 1.

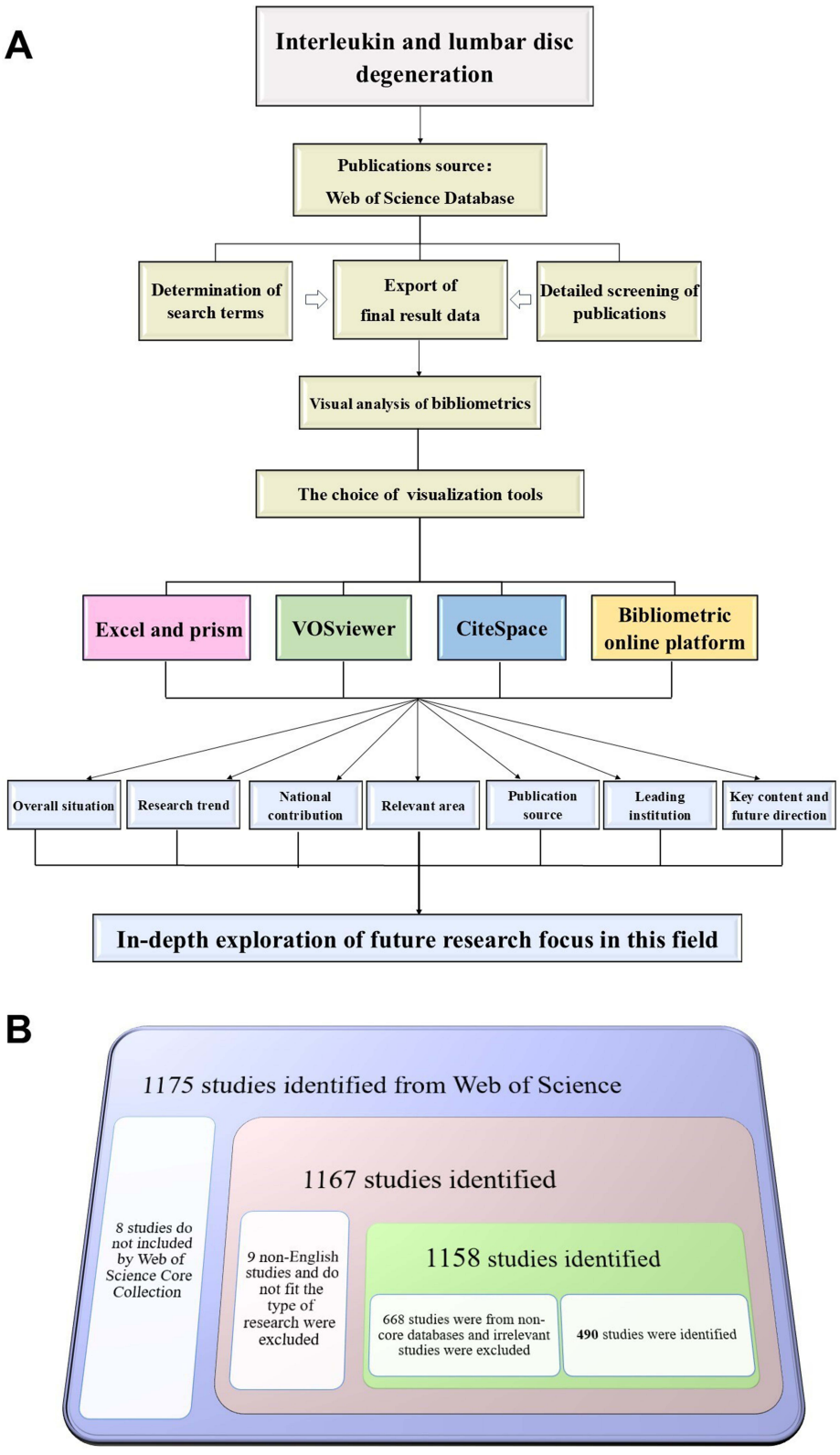

Figure 1 Flow diagram of the inclusion process. (**A**) The detailed process of screening and enrolment is shown. (**B**) The detailed process of screening and inclusion. Irrelevant articles were manually screened by two authors through their abstracts and full texts, and articles irrelevant to the topic were excluded.

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Data Collection

General information about the title, keywords, author, publication date, country and region of origin, institutions, periodicals, cited times of articles, H index, etc. Extracted from the publications identified by three authors. Several data analysis tools are used for data analysis and processing, such as GraphPad Prism 8, Microsoft Excel 2016, VOSviewer version 1.6.12, CiteSpace version 5.6. R5 64 bit, and an online analysis platform (http://bibliometric.com/) were used for presenting, analyzing, and describing the data.[25]

Reference Analysis

Web Science (WOS) is a database covering the research of life medicine, so our bibliometrics chooses the database of WOS. There are some important indicators for evaluating the quality of articles, including impact factor (IF), H index, relative research interest (RRI) and Average citation. According to the situation of this study, because there are not many qualified articles, we choose the impact factor (IF), H index and Average citation, which are our main research contents. Generally speaking, we can think that the influence factor can directly reflect the quality and influence of an article. The H index of an article can be used as a measure of academic productivity and an objective index to evaluate the quality of the article. It can reflect that a scholar or country has published at least H papers on a specific topic, and each paper has been cited at least H times. Average citation can reflect the number of times a country's articles are cited, and it is also an index to measure the recognition of a country's scientific research literature by other countries or institutions.

VOS viewer is a practical statistical software, which can visually analyze references, institutions, authors and terms by using the text downloaded by WOS. The software shows the time distribution and dynamic variability of keywords, and accurately reveals the evolution trend of hot topics in the research field. CiteSpace uses Java programming language, which is a useful tool for data analysis and processing, and is widely used for co-citation network analysis and visualization.

Result

From 1 January 2015–1 December 2024 a total of 490 articles met our inclusion criteria (excluding 23 articles not collected by WOS database; 668 non-English articles were excluded because they did not meet the type requirements; And 1839 articles were excluded because they were irrelevant to the topic) (Figure 1B). This research focuses on five aspects: the contribution of the country, the contribution of different journals, the contribution of different institutions, keywords and related fields.

Publication Growth Trend

The cumulative number of publications in the world and the corresponding model fitting curve are shown in Figure 2. According to these growth curves, we find that the global publications are growing very rapidly. By comparing the number of papers published each year, we can easily find that the largest number of papers was published in 2024, with 65 papers (Figure 2A). According to the annual distribution of publications, we found that since 2015, researchers' interest in the involvement of interleukin family cytokines in intervertebral disc degenerative diseases has basically shown an upward trend, so the number of published articles almost showed an overall upward trend, except that the number of articles published in 2022 and 2023 decreased slightly, which reached the highest peak so far in 2024. Looking forward to this trend, we predict that by 2038–2043, the number of articles published in these five years may exceed 100, or even approach 160 (Figure 2B). This trend highlights the increasing popularity of research in this field in the next 20 years.

Global Contribution to This Field

Judging from the global distribution of publications, China ranks first in the number of publications, with 280 kinds; Followed by the United States (79 publications), Japan (36 publications), Britain (27 publications) and Germany (27 publications) (Figure 3A). The top 10 countries with the largest number of publications are shown in Figure 3B and Table 1.The top five countries/regions with total citations are 286 in the United States, 284 in China, 146 in Britain, 67 in Japan and 31 in Germany. The countries/regions with the highest H index are as follows: China 200, the United States 185, Britain 115, Japan 95 and Germany 80 (Figure 3B). The cooperation between countries/regions is

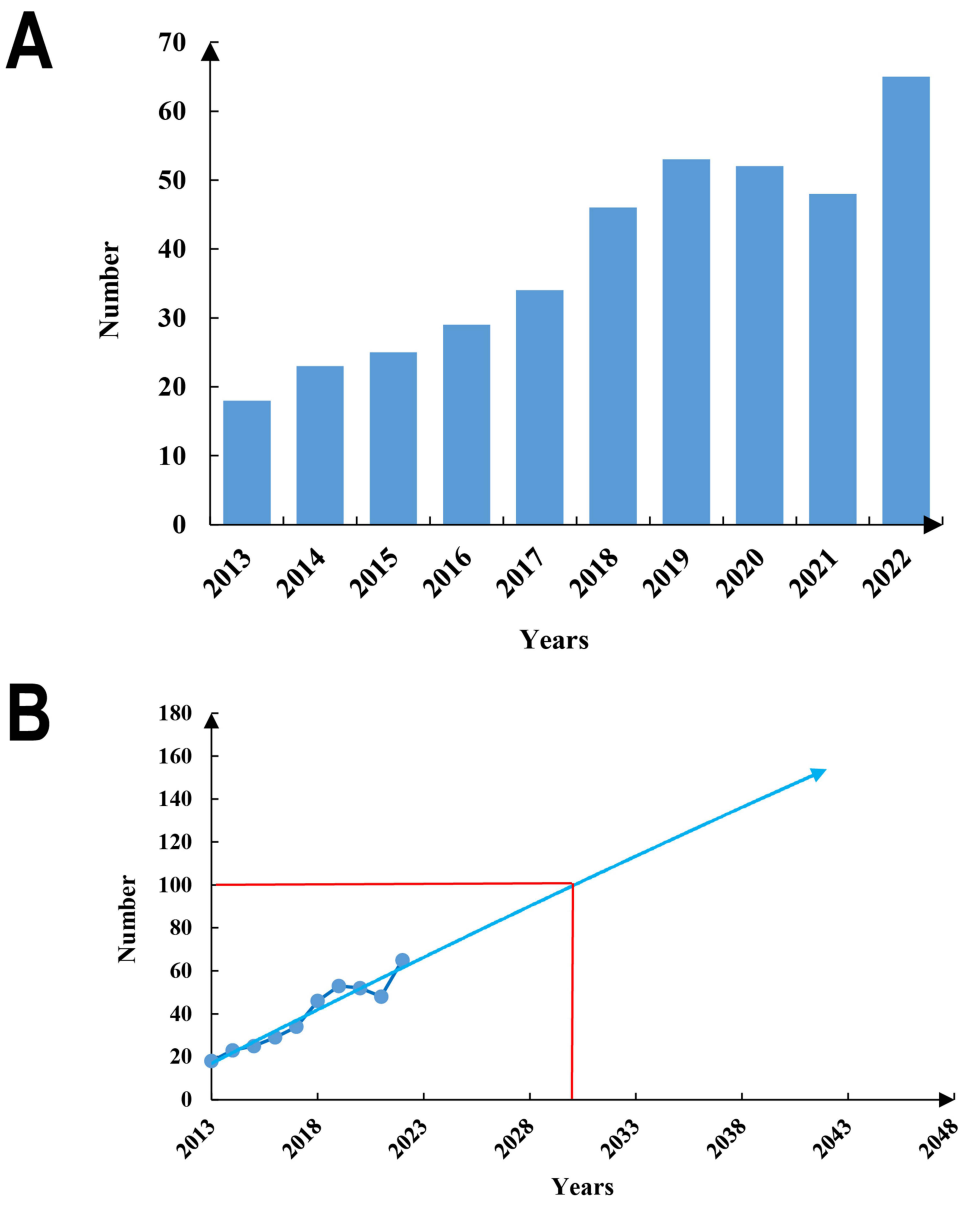

Figure 2 Analysis on the trend of publishing articles in the research on Interleukin and Intervertebral Disc Degenerative Diseases. (**A**) Global number of articles published in this field from 2015 to 2024. (**B**) Analysis on the trend change of global papers published in this field from 2015 to 2024.

shown in Figure 3C-D, where the size of the circle indicates the number of publications and the width of the connecting line between the two circles indicates the degree of cooperation. In many countries/regions, the output time is relatively concentrated. For example, most publications in the United States were published before 2018, mainly in 2014–2016, while China is the country with the largest number of publications, but most of them were published after 2018, which also shows that although China started late in this field, China's research results are relatively novel, which can represent the latest research direction in this field to a certain extent (Figure 3C). China and the United States have the largest number of publications in this field, the most cooperation in this field, and the strongest overall link strength. The cooperative efforts of various countries have further emphasize the leading position of China and the United States. These cooperations have improved the overall quality of research in this field. (Figure 3B).

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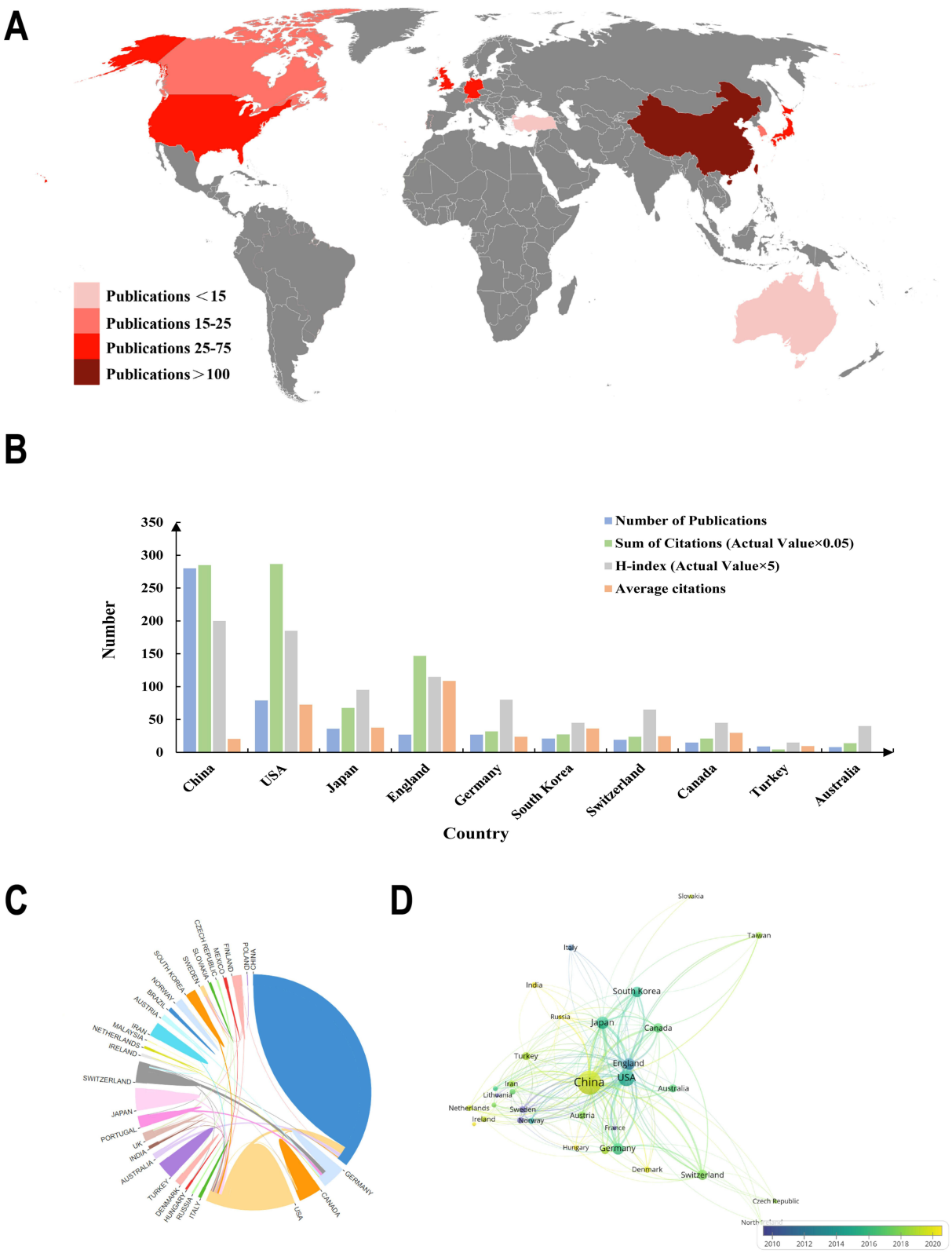

Figure 3 Contributions of different countries/regions to the research on Interleukin and Intervertebral Disc Degenerative Diseases. (**A**) According to the visual statistics of the country/region, the darker the color, the greater the number of posts, and the lighter the color, the smaller the number of posts. (**B**) Number of publications, citation frequency (×0.05), and H-index (×5) in the top 10 countries or regions; (**C**) Network of cooperative relations between countries/regions established by VOSviewer; (**D**) visualized cooperative relations between countries/regions.

Table 1 Top 10 Nations That Publish Articles on Interleukin and Intervertebral Disc Degenerative Diseases

SCR[a]	Country	Contribution (Number)	Sum of Citations (Actual Value×0.05)	H-index (Actual Value×5)
First	China	280	284.85	200
Second	United States of America	79	286.55	185
Third	Japan	36	67.65	95
Fourth	England	27	146.85	115
Fifth	Germany	27	31.95	80
Sixth	South Korea	21	27.2	45
Seventh	Switzerland	19	23.65	65
Eighth	Canada	15	20.85	45
Ninth	Turkey	9	4.3	15
Tenth	Australia	8	13.75	40

Abbreviation: aSCR, Standard competition ranking.

Institutions That Study This Field

China's Huazhong Univ Sci & Technol has published the most papers among institutions in the world, with a total of 24 papers, followed by Shanghai Jiao Tong Univ (22 articles, Wenzhou Med Univ (18 articles), Zhejiang Univ (18 articles) and Soochow Univ (15 articles). Among the top 20 institutions in this field, institutions in China account for more than half, and among the top 10 institutions, there are 9 in China (Figure 4A and Table 2); In addition, three institutions are in the United States, two in Switzerland, and one in Britain, Japan and Canada. We can not only analyze the total number of articles published by different institutions, but also analyze the cooperation relationship and degree between various institutions. Figure 4B highlights the close and complicated cooperation relationship between different institutions. VOS viewer is used to analyze the centrality of these mechanisms. The circle represents the centrality, and the area of the circle is directly proportional to its centrality. Asterisks of the same color indicate that these organizations belong to the same organization. Huazhong Univ Sci & Technol and Shanghai Jiao Tong Univ are the most famous institutions, which shows that they are regarded as key points.

Analysis of Periodical Distribution

Nearly one third of the articles were published in 10 journals (133 articles)(Table 3). Among them, the number of articles published in Spine journal is the largest, with 30 records, and the number of publications of Arthritis Research & Therapy ranks second (Figure 5A). The top two journals in IF are Arthritis Research & Therapy (IF = 9.0) and International Journal of Molecular Sciences (IF = 5.6), with 19 articles and 8 articles respectively, ranking second and tenth respectively. It is worth noting that the comprehensive index of Arthritis Research & Therapy also ranks first. The result is visualized in Figure 5B, where the size of the circle represents the number of publications.

Related Field Analysis

As shown in Figure 5C, the 490 publications we studied are mainly divided into three fields. The first field includes Medicine, Medical, Clinical; The second field includes Molecular, Biology, Immunology; The third area includes Psychology, Education, Health. The references of these 490 articles are mainly distributed in the following fields: Molecular, Biology, Genetics, and Health, Nursing, Medicine. We found that the correlation between interleukin family cytokines and intervertebral disc degeneration mainly involved in medicine, health, biology, molecular and other fields. The further research and development in this field is related to the combination of medical and immune related disciplines.

Commonality Analysis of Keywords

We used VOS viewer to analyze the keywords extracted from 490 publications. Out of a total of 194 keywords, four keywords have the highest frequency, which include intervertebral disc degeneration (including intervertebral disc

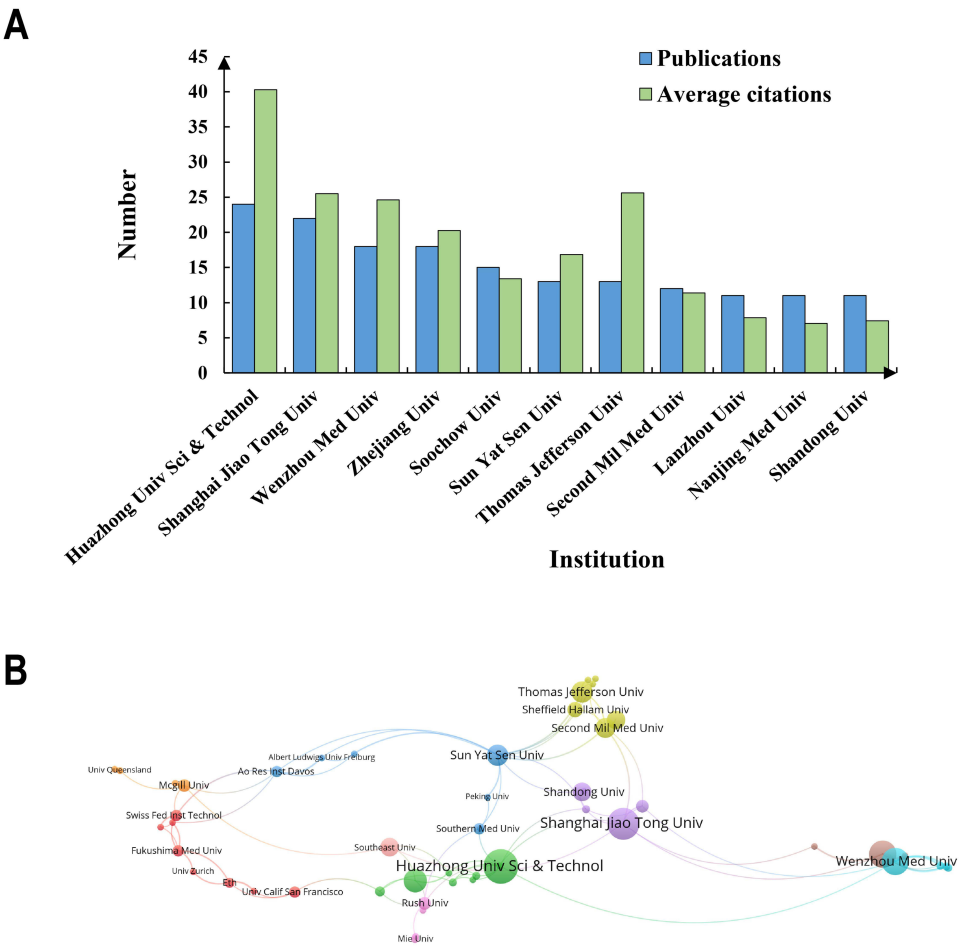

Figure 4 Distribution of institutions engaged in research on Interleukin and Intervertebral Disc Degenerative Diseases. (**A**) Top 10 institutions by number of publications. The numbers represent the percentage of publications, and different colors represent different countries. (**B**) Network of institutions visualized in VOSviewer. The size of circles represents the number of publications.

degeneration, degenerative disc disease, Lumbar disc degeneration and disc degeneration) (246 times), nucleus pulposus cells (including nucleus pulposus cells and nucleus pulposus) (201 times), Expression (including cytokine expression) (197 times), interleukin-1 (il-1-beta, il-1beta, interleukin-1-beta, interleukin-1beta, interleukin-1 and il-1) (130 times). Figure 6A shows the detailed data of concurrency of all included keywords. The co-occurrence analysis of keywords is

Table 2 Top 10 Institutions That Publish Articles on Interleukin and Intervertebral Disc Degenerative Diseases

SCR[a]	Institution	Contribution (Number)	Country
First	Huazhong Univ Sci & Technol	24	China
Second	Shanghai Jiao Tong Univ	22	China
Third	Wenzhou Med Univ	18	China
Fourth	Zhejiang Univ	18	China
Fifth	Soochow Univ	15	China
Sixth	Sun Yat Sen Univ	13	China
Seventh	Thomas Jefferson Univ	13	United States of America
Eighth	Second Mil Med Univ	12	China
Ninth	Lanzhou Univ	11	China
Tenth	Nanjing Med Univ	11	China

Abbreviation: aSCR, Standard competition ranking.

Table 3 Top 10 Journals That Publish Articles on Interleukin and Intervertebral Disc Degenerative Diseases

SCR[a]	Journal	Contribution (Number)	IF[b]
First	Spine	30	3
Second	Arthritis research and therapy	19	9
Third	Scientific reports	14	4.6
Fourth	European spine journal	12	2.8
Fifth	Experimental and therapeutic medicine	11	2.7
Sixth	Journal of orthopaedic research	11	2.8
Seventh	Molecular medicine reports	10	3.4
Eighth	European review for medical and pharmacological sciences	9	3.3
Ninth	Spine journal	9	4.5
Tenth	International journal of molecular sciences	8	5.6

Note: bIF, Impact factor (The impact factors are reported according to the 2022 Journal Citation Report (JCR)).
Abbreviations: aSCR, Standard competition ranking.

helpful for scholars to systematically understand the relationship between keywords. Further cluster analysis is helpful for us to systematically understand the current progress in this field. As shown in Figure 6A and B, VOS viewer colorizes all keywords according to the average times and time of their appearance. Specifically, purple indicates that the keyword

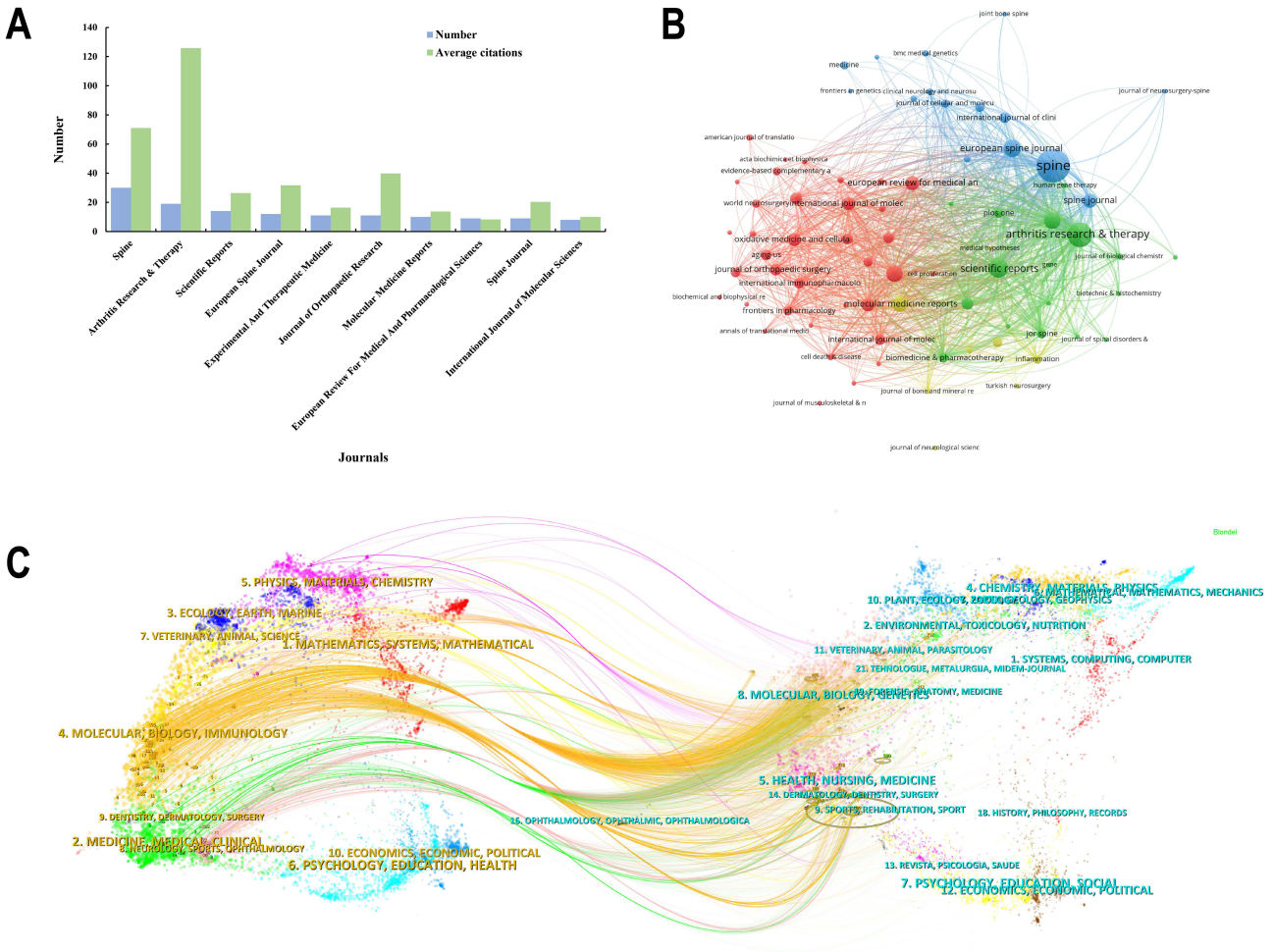

Figure 5 Distribution of journals engaged in research on Interleukin and Intervertebral Disc Degenerative Diseases. (**A**) Top 10 journals by number of publications. Numbers represent the percentage of publications, and different colors represent different countries; (**B**) network of journals visualized in VOSviewer. The size of the circles represents the number of publications; (**C**) Related fields of Interleukin and Intervertebral Disc Degenerative Diseases, the left is the literature included in this study, and the right is the reference of this literature.

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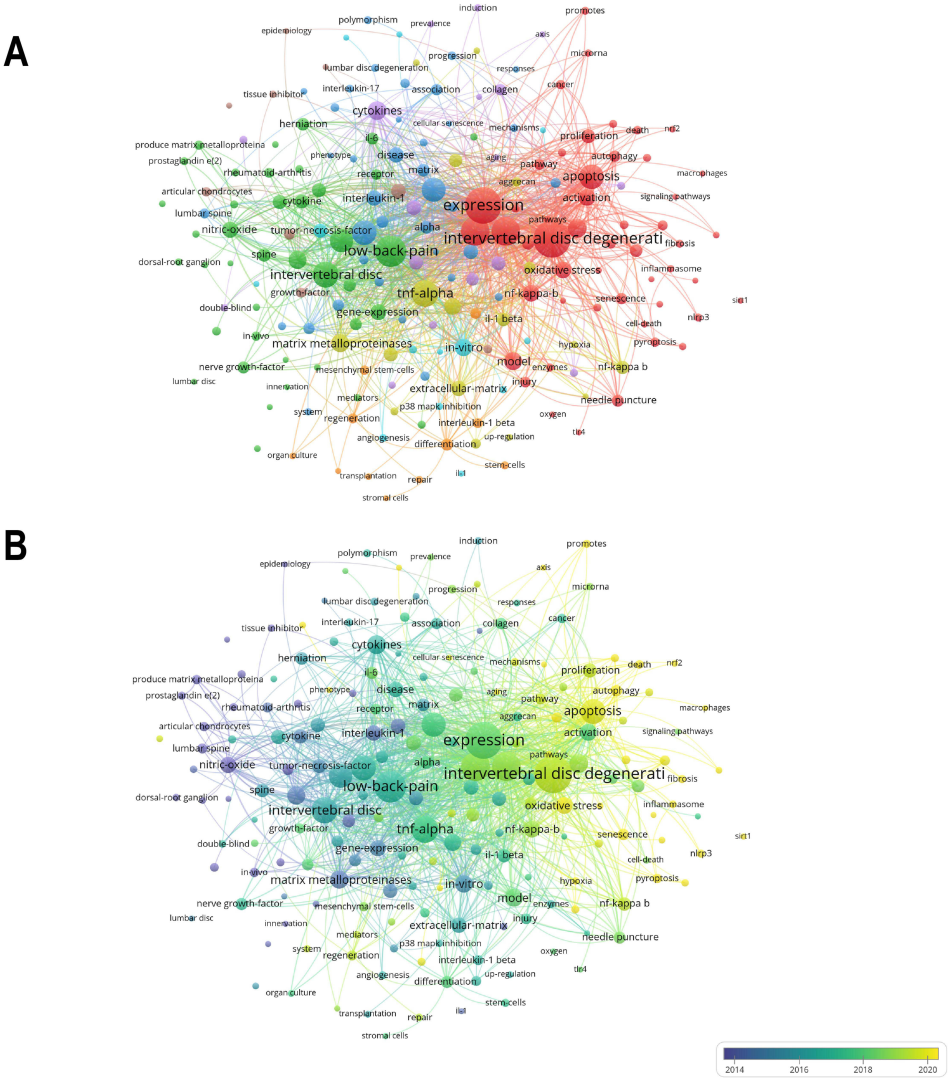

C Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1996 - 2023
articular chondrocytes	1996	2.65	**1996**	2005	
cartilage	1997	3.19	**1997**	2009	
low back pain	1996	4.83	**2005**	2007	
disc degeneration	2007	5.21	**2007**	2015	
necrosis factor alpha	2007	4.26	**2007**	2011	
matrix metalloproteinases	2009	9.63	**2009**	2016	
nucleus pulposus	2004	3.22	**2012**	2015	
disease	2015	4.07	**2015**	2017	
il-1 beta	2015	3.49	**2015**	2018	
tnf-alpha	2013	4.6	**2016**	2018	
cytokines	2017	3.57	**2017**	2020	
il-1	2018	4.15	**2018**	2021	
model	2014	4.56	**2019**	2021	
oxidative stress	2020	6.87	**2020**	2023	
apoptosis	2019	6.73	**2020**	2023	

Figure 6 Co-occurrence analysis of all keywords in the publications on Interleukin and Intervertebral Disc Degenerative Diseases. (**A**) Mapping of the keywords in the field of Interleukin and Intervertebral Disc Degenerative Diseases. The size of the circle represents the frequency of the keyword, and different colors represent different clusters. (**B**) Distribution of keywords according to the average time of appearance. Purple represents an early appearance, and yellow represents a late appearance. (**C**) Top 15 keywords cited most frequently from 1996 to 2020, which have received continuous attention for a period of time. The red bars represent frequently cited keywords during this time period, and the green bars represent infrequently cited keywords.

appears relatively early, while yellow indicates that the keyword appears later. Different from the most frequent keywords, the latest keywords can often represent the current research hotspots in this field, which is also the place that most scholars are interested in. It's not hard to find that Apoplexy, oxidative, autophagy are the latest hot topics in this field. Figure 6C shows other information of keywords. The most notable keyword is Matrix Metaloproteinas, with an intensity of 9.63. From 2009 to 2016, it became more important. Recently, the latest notable keywords are apoptosis and oxidative stress. From 2020 to 2023, their importance is increasing, with intensities of 6.73 and 6.87 respectively. Keywords such as cartilage and articular chondrocytes have the longest popularity (12 years and 9 years respectively), and their intensity enhancement stages are 1997 ∽2009 and 1996 ∽2005 respectively. This is because the interleukin family cytokines mainly control the decomposition process of the extracellular matrix (ECM) of intervertebral disc by regulating matrix metalloproteinases (MMPs). Moreover, its main cell is nucleus pulposus cells, which can regulate the oxidative stress reaction in nucleus pulposus cells and ultimately affect the progress of intervertebral disc degeneration.

Financial Support in This Field

Supplement Figure 1 analyzes the financial support of the included literature. Among them, the National Natural Science Foundation (NSFC) provides the most funding, followed by the National Institutes of Health (NIH) and the UNITED STATES DEPARTMENT OF HEALTH HUMAN SERVICES (HHS), which represent the frontiers of scientific research and development in China and the United States, respectively. Both national institutions provide financial assistance for the research of interleukin and intervertebral disc degeneration treatment, which reflects the affirmation of the development prospects of the two countries in this field.

Discussion

Research Trend of Interleukin Family Cytokines Regulating Intervertebral Disc Degenerative Diseases

China has contributed the most to the publishing volume of all countries (Figure 3A), and its share in global output far exceeds the second place, which shows that China attaches great importance to scientific research in this field (Figure 3B), and the H index of publications published in China is also the highest, which shows that China's publications have great influence all over the world. The United States is close behind. Although the publication volume of the United States is much smaller than that of China, its total cited volume and H index are almost the same as those of China, indicating that the overall quality of publications in the United States is better. Based on WOS data, the national contact map shows that China and many countries are active in this field, especially the United States, which have the most publications, which also shows that mutual cooperation plays an important role in promoting the development of this field. Moreover, China not only ranks first in the number of publications and the H index, but most of the publications in China are after 2018, which also reflects the novelty of China's research results. The United States and Britain ranked second and third, although their research results are mostly before 2018, it can also reflect that these countries started their research in this field earlier, which has made important preparations for further research in this field.

Regarding research institutions, the national results are also very important. Nine of the top 10 institutions are from China (Figure 4A and B), and the latest research results are all from China, and there is a certain cooperative relationship between these institutions (Figure 4B). This shows that China is playing an increasingly important role in this field and has become a new research center. In terms of periodicals, it mainly includes clinical medicine and biomedicine, which mainly includes the combination of spinal surgery, sports medicine, molecular biology and immunology (Figure 5A and B). This shows that the development of this field needs interdisciplinary cooperation. Moreover, more than 25% of the literatures are published in the top ten journals, among which spine, arthritis research and therapy and scientific reports rank in the top three, so authors in this field can get the latest research progress of interleukin family cytokines regulating intervertebral disc degeneration from these journals in time.With the increasing incidence of intervertebral disc degeneration in recent years, academic interest is also increasing steadily. In our view, there are two main reasons for this widespread concern. On the one hand, researchers have made deeper study on the pathogenesis of intervertebral disc degeneration, and realized that intervertebral disc degeneration is closely related to the inflammatory reaction of related

tissues, which is probably the main pathogenesis of intervertebral disc degeneration, and inflammatory reaction produces a large number of cytokines and plays an important role in the process of intervertebral disc degeneration; On the other hand, the interleukin family is a star family of inflammatory cytokines. In recent years, more and more interleukin family cells have been proved to be closely related to the occurrence and development of intervertebral disc degeneration, and they can finally realize the pathological adjustment of intervertebral disc degeneration through different signal pathways.

Research Progress of Interleukin Family Cytokines in Clinical Diagnosis of Intervertebral Disc Degeneration

This study found that intervertebral disc degeneration, nucleus pulposus cell, expression and interleukin-1 have become the focus of clinical attention in recent years. In fact, intervertebral disc degeneration is the research subject in this field, and this study mainly focuses on the disease. Nucleus pulposus cell is the main acting cell of intervertebral disc degeneration, and the pathological changes of intervertebral disc degeneration are mainly caused by apoptosis of nucleus pulposus cell. Expression and interleukin-1 show the actual process of this field, that is, the expression of interleukin cytokines can affect the nucleus pulposus cell, and ultimately affect the process of intervertebral disc degeneration, and interleukin-1 is undoubtedly the most important member of the interleukin family in this field.

The Role of Intervertebral Disc and Nucleus Pulposus Cells in This Field

Intervertebral disc is a soft tissue structure located between the upper and lower vertebral bodies, which consists of nucleus pulposus (NP), annulus fibrosus (AF) and cartilage endplate (CEP). Intervertebral disc plays an important role in buffering pressure, maintaining the stability of spine, maintaining the physiological curvature of spine and the flexibility of spine. Intervertebral disc is mainly composed of collagen, proteoglycan, elastic fiber, non-collagen protein and glycoprotein.[26–29] The nucleus pulposus mainly contains type II collagen without type I collagen, and the type I collagen in the annulus fibrosus gradually decreases from the outside to the inside, while the type II collagen and proteoglycan tend to increase. In the process of intervertebral disc degeneration, the nucleus pulposus is fibrotic and torn, and the pathological changes of nucleus pulposus occupy the dominant position in the degeneration process. In this process, the intervertebral disc matrix is destroyed, the water content decreases and the viscoelasticity decreases. With the further development of the lesion, the degree of nuclear fibrosis is further aggravated. Therefore, it is believed that the core of intervertebral disc degeneration lies in the inflammatory reaction and apoptosis of nucleus pulposus cells.[4,30–32] Intervention of nucleus pulposus cells has gradually become an important means to treat intervertebral disc degeneration.

Interleukin Factor Is Involved in the Development of Intervertebral Disc Degeneration

Previous studies have confirmed that inflammatory reaction is probably the main pathogenesis of intervertebral disc degeneration, and a large number of cytokines produced by inflammatory reaction play an important role in the process of intervertebral disc degeneration.[33] At present, there are more than 100 kinds of cytokines, such as interleukin family cytokines, tumor necrosis factor (TNF-α), colony stimulating factor (CSF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (POGF) and fibroblast growth factor. Interleukin is a kind of cytokine produced by and acting on various cells. Up to now, 38 interleukins, IL-1∽38, have been found. Their functions are diverse, networked and complicated, and they participate in many physiological and pathological reactions.[34] Here is a brief analysis of that mechanism of interleukin family cytokine in intervertebral disc degeneration (Figure 7 and Table 4).

As an interleukin cytokine closely related to intervertebral disc degeneration, IL-1β can stimulate intervertebral disc cells to produce a large number of chemokines, including monocyte chemotactic proteins (MCP-1, MCP-3, MCP-4), thus promoting the aggregation of macrophages, neutrophils and T lymphocytes in peripheral blood in the intervertebral disc tissue and accelerating the intervertebral disc degeneration.[35] At the same time, IL-1β can promote the secretion of matrix metalloproteinases (MMPs) and disintegrin and metalloproteinase with thrombospondin motif (ADAMTs), which will lead to the decrease of the expression of Aggrecan and Collagen-II, and further accelerate the degeneration of intervertebral disc.[19] IL-1β may also lead to an increase in the release of inflammatory corpuscles of NLRP3, forming IL-1β-NLRP3 inflammatory complex and aggravating intervertebral disc degeneration.[36] The study also showed that IL-1β mainly caused intervertebral disc degeneration by activating NF-kB and MAPK signaling pathways.[37,38] IL-2 can

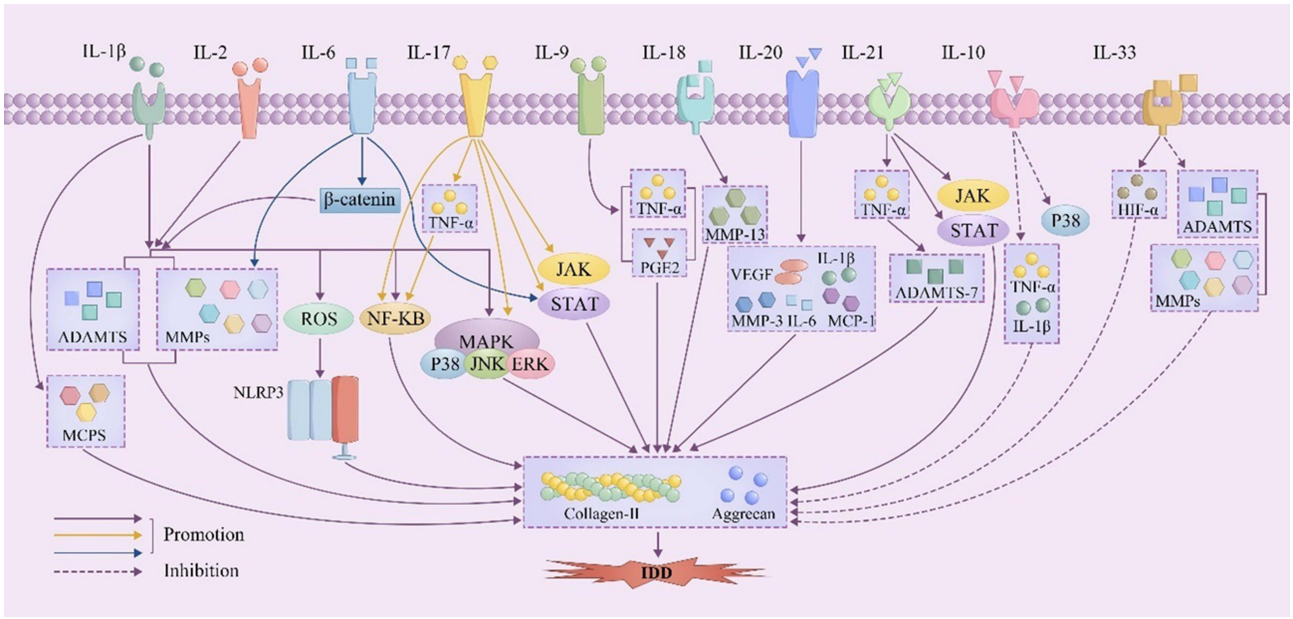

Figure 7 Mechanism analysis of interleukin family cytokines regulating intervertebral disc degeneration. IL-1, IL-2, IL-6, IL-9, IL-17, IL-18, IL-20 and IL-21 in the interleukin family mainly cause inflammatory reaction, promote MMPs and ADAMTSs, cause the degradation of intervertebral disc ECM, at the same time lead to the apoptosis of intervertebral disc cells, and aggravate the pathological process of intervertebral disc degeneration. IL-10 and IL-33 play a certain inhibitory role in the process of intervertebral disc degeneration.

activate P38-MAPK signal pathway in nucleus pulposus cells and cause intervertebral disc degeneration. At the same time, the expression levels of ADAMT-4, 5, MMP-3 and 13 are obviously increased and the expression level of Collagen-II is decreased after IL-2 treatment of nucleus pulposus cells.[22] IL-6 is also involved in intervertebral disc degeneration. IL-6 can promote the expression of MMPs, activate STAT3 in nucleus pulposus cells and annulus fibrosus

Table 4 Mechanism of Interleukin Family Cytokines in Intervertebral Disc Degeneration

Classify	Name	Mechanism
Promoting factor	IL-1β	IL-1β can stimulate the production of MCP-1, MCP-3 and MCP-4 in intervertebral disc cells, and promote the secretion of matrix metalloproteinases (MMPs) and depolymerized protein-like metalloproteinases (ADAMTs). IL-1β may also increase the release of inflammatory bodies of NLRP3 and form IL-1β-NLRP3 inflammatory complex. IL-1β mainly causes intervertebral disc degeneration by activating NF-kB and MAPK signaling pathways.[19,35–38]
	IL-2	IL-2 can activate P38-MAPK signal in nucleus pulposus cells, and also lead to a significant increase in the expression levels of ADAMT-4, 5, MMP-3 and 13.[22]
	IL-6	IL-6 can promote the expression of MMPs and activate STAT3 in nucleus pulposus cells and annulus fibrosus cells, and IL-6 can also activate β-catenin signaling pathway, resulting in the increased expression of MMP-13 and ADAMT-5.[20,39]
	IL-9	IL-9 promotes the increase of tumor necrosis factor-α (TNF-α) and prostaglandin E2(PGE2) in nucleus pulposus cells.[23]
	IL-17	IL-17 activates the JAK/STAT pathway and P38 or JNK pathway in nucleus pulposus cells, and it also activates NF-kB by promoting the release of TNF-α or directly activates NF-kB signaling pathway, leading to the up-regulation of MMP-13.[40–43]
	IL-18	IL-18 decreased the expression of Aggrecan and Collagen-II in nucleus pulposus cells and annulus fibrosus cells.[44]
	IL-20	IL-20 promoted the expression of IL-1, IL-6, VEGF, MMP-3 and MCP-1.[45]
	IL-21	IL-21 promotes the secretion of TNF-α to increase the expression of ADAMTS-7, and IL-21 may lead to intervertebral disc degeneration by activating JAK-STAT signaling pathway.[46,47]
Inhibitor	IL-10	IL-10 can reduce the expression levels of IL-1β and TNF-α, and inhibit the activation of P38-MAPK signaling pathway to alleviate the process of intervertebral disc degeneration.[48–50]
	IL-33	IL-33 upregulates the expression of hypoxia-inducible factor 1α (HIF-1α) and reduces the release of MMP-3, 13 and ADAMTS-4, 5 in nucleus pulposus cells.[24]

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cells, and then induce intervertebral disc degeneration.[39] Moreover, IL-6 can also activate β-catenin signaling pathway, causing the expression of MMP-13 and ADAMT-5 to increase, thus causing the degradation of Aggrecan and Collagen-II.[20] IL-9 can promote the increase of tumor necrosis factor-α (TNF-α) and prostaglandin E2(PGE2) in nucleus pulposus cells, which indicates that IL-9 is involved in the process of intervertebral disc degeneration.[23] The expression of IL-17 is up-regulated in human degenerative intervertebral disc tissue.[40] Studies show that IL-17 up-regulates the expression of vascular endothelial growth factor (VEGF) by activating JAK/STAT pathway in nucleus pulposus cells, which aggravates intervertebral disc degeneration.[41] IL-17 can not only activate NF-kB by promoting the release of TNF-α, but also directly activate NF-kB signaling pathway, which will lead to the up-regulation of MMP-13 and the degradation of Aggrecan and Collagen-II.[42] At the same time, IL-17 can also mediate inflammatory reaction in nucleus pulposus cells through P38 or JNK pathway.[43] The content of IL-18 in the serum of patients with intervertebral disc degeneration increased significantly. After IL-18 acts on nucleus pulposus cells and annulus fibrosus cells, it affects the biosynthesis of nucleus pulposus cells and annulus fibrosus cells by reducing the contents of aggrecan and collagen-II, which leads to the degradation of extracellular matrix and eventually leads to disc degeneration.[44] The expression of IL-20 is significantly related to the degree of intervertebral disc degeneration. IL-20 can increase the expression of IL-1, IL-6, VEGF, MMP-3 and MCP-1, thus promoting the degradation of Aggrecan and Collagen-II and aggravating intervertebral disc degeneration.[45] IL-21 can increase the expression of ADAMTS-7 in intervertebral disc tissue by promoting the secretion of TNF-α, thus aggravating the degeneration of intervertebral disc.[46] Of course, some scholars believe that IL-21 may lead to intervertebral disc degeneration by activating JAK-STAT signaling pathway.[47]

In addition to the above proinflammatory cytokines, several members of the interleukin family may have the effect of inhibiting intervertebral disc degeneration. As an anti-inflammatory cytokine, studies have confirmed that IL-10 is expressed in serum and intervertebral disc tissues of patients with intervertebral disc degeneration.[48] IL-10 can alleviate the inflammatory reaction of intervertebral disc by reducing the expression levels of IL-1β and TNF-α.[49] Moreover, experiments have confirmed that IL-10 can significantly reduce the phosphorylation level of P38 and inhibit the activation of P38-MAPK signaling pathway to alleviate the process of intervertebral disc degeneration.[50]

In the nucleus pulposus of patients with intervertebral disc degeneration, the expression level of IL-33 gradually decreases with the increase of intervertebral disc degeneration, and previous studies have confirmed that IL-33 can up-regulate the expression of hypoxia-inducible factor 1α(HIF-1α). HIF-α has been proved to promote the synthesis of extracellular matrix and significantly increase the expression of Collagen-II and Aggrecan in nucleus pulposus cells. This study also confirmed that the over-expression of IL-33 can reduce the expression of collagen-II and Aggrecan in nucleus pulposus cells.[24]

Study and Analysis of Interleukin Family Cytokines in the Treatment of Intervertebral Disc Degeneration

With the in-depth study of the mechanism of intervertebral disc degeneration, some treatments for related interleukin cytokines have also made considerable progress. Researchers can inhibit the synthesis of pro-inflammatory factors (IL-1β, IL-6, etc.)[51,52] and promote the synthesis of anti-inflammatory cytokine (IL-10) through stem cell transplantation.[53] Gene modification technology has also made a breakthrough. Cambria et al have studied the genes that TNFR4 regulates the expression of IL-6 and IL-8 through CRISPR gene editing system, and reduced the risk of severe chronic inflammation caused by supraphysiological stretching of annulus fibrosus cells.[54] Some scholars have also verified the feasibility of MiRNA technology in this field. For example, inhibiting miR-34a can prevent IL-1β-induced inhibition of type II collagen synthesis in chondrocytes;[55,56] Inhibition of miR-15b can reduce the excessive production of IL-1β by increasing the expression of SMAD-3, and then reduce the degradation of extracellular matrix in nucleus pulposus cells;[57] The introduction of miR-202-3p can inhibit the production of MMP-1 induced by IL-1β.[58] The introduction of miR-10a-5p can inhibit IL-6-induced ferroptosis of cartilage cells.[59]

In addition to these in vivo pathways, in vitro therapy has also attracted the attention of researchers. Exosomes derived from bone marrow mesenchymal stem cells can reduce the over-expression of proinflammatory factors induced by IL-1β and inhibit MAPK signaling pathway;[60,61] However, the intervention of exosome miR-410 from mesenchymal

stem cells can significantly reduce the expression of NLRP3 inflammatory corpuscles and the activation of caspase, thus inhibiting the secretion of pro-inflammatory cytokines (IL-1β, IL-18, etc).[62,63] Exosome from ADSC also have similar effects, which lead to the inactivation of NLRP3 inflammatory corpuscles and inhibit the release of pro-inflammatory cytokines (IL-1β and IL-6).[64]

These studies have analyzed the influence of interleukin cytokines on intervertebral disc degeneration from different angles (Table 5), and all kinds of studies are still deepening and related technologies are constantly developing, which provides a solid theoretical and practical basis for the treatment of intervertebral disc degeneration diseases with interleukin cytokines.

Research Significance

This article is the first bibliometric analysis that focuses on the regulation of intervertebral disc degeneration by interleukin family cytokines. The data analysis of the full text is relatively comprehensive and objective. The results not only reveal the most influential countries and institutions in this field at present, but also analyze the mechanism of related cytokines in the process of intervertebral disc degeneration. This has certain reference value for future academic research or communication on the treatment of intervertebral disc degeneration through the mechanism of interleukin cytokines. Moreover, the research on targeted therapy of interleukin-cytokines is becoming more and more popular, which also shows that the research in this field can indeed become another new method for the treatment of intervertebral disc degeneration. At the same time, through the objective analysis of China's literature changes in this field, the great contribution of Huazhong Univ Sci & Technol in this field is further clarified, which also provides a place for scholars to study and discuss the treatment of intervertebral disc degeneration with interleukin cytokines in the future.

Restriction

In this study, the publications in WOS database were investigated, so that objective and accurate results can be obtained. In previous reports, scholars have confirmed that document type tags are more accurate than Scopus, so we give priority to WOS-based retrieval.[65] However, the WOS database is regularly updated. After the database is constantly updated, our results may be slightly different from the actual situation. Moreover, citation data will be influenced by many factors,

Table 5 High-Tech Medical Technology Is Used to Correct the Imbalance of Interleukin and Cytokine in Patients with Intervertebral Disc Degeneration

Method	Mechanism of Action
Stem cell implantation	Inhibit the synthesis of pro-inflammatory factors (IL-1β, IL-6, etc.) and promote the synthesis of anti-inflammatory cytokine (IL-10).[51–53]
Gene modification	The expression of IL-6 and IL-8 regulated by TNFR4 was studied by CRISPR gene editing system.[54]
MicroRNA	Inhibition of miR-34a can inhibit the biological activity of IL-1β and increase the content of type II collagen in intervertebral disc tissue.[55,56]
	Inhibition of miR-15b can increase the expression of SMAD-3, thus reducing the overproduction of IL-1β, and further reducing the degradation of extracellular matrix in nucleus pulposus cells.[57]
	Over-expression of miR-202-3p can inhibit the activity of IL-1β, thus reducing the production of MMP-1.[58]
	Over-expression of miR-10a-5p can inhibit the biological activity of IL-6.[59]
Exosomes derived from bone marrow MSCs (BMSC-Exos)	Inhibition of IL-1β-induced of pro-inflammatory cytokines overexpression. Meanwhile, it can also inhibit the activation of MAPK signaling pathway;[60,61].
Exosomal miR-410 derived from MSCs	Significantly reduce the expression of inflammatory corpuscles of NLRP3 and the activation of caspase, thus inhibiting the secretion of pro-inflammatory cytokines (IL-1 β, IL-18, etc).[62,63]
Exosomes derived from ADSC	Inactivation of NLRP3 inflammasome and related pro-inflammatory cytokines release (IL-1β, TNF-α, and IL-6).[64]

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such as self-citation, language bias and citation practice in different disciplines, which may affect the effectiveness of bibliometric analysis. Journal impact factors and other journal-level indicators are criticized because they may be abused when evaluating individual researchers or articles, because they do not always reflect the real impact of specific research. Finally, the dependence on quantitative data in bibliometrics may not capture the whole range of research quality and influence, and qualitative factors, such as research design, methods and social influence, must be considered. In addition, in order to obtain more comprehensive results, Scopus and Google Scholars can be included in future research for comparison. Due to the characteristics of database retrieval, we cannot analyze the research hotspots and future trends of interleukin family cytokines in intervertebral disc degeneration diseases in detail, and hope to make a more detailed analysis in future research.

Conclusion

With the in-depth study of the pathogenesis of intervertebral disc degeneration, some cytokine therapy methods for intervertebral disc degeneration have made some progress. Interleukin family, as a highly regarded member of cytokines, plays an important role in the mechanism of intervertebral disc degeneration. Most interleukin cytokines mainly cause inflammatory reaction, promote the release of MMPs and ADAMTSs, cause the degradation of extracellular matrix of intervertebral disc, and lead to the apoptosis of intervertebral disc cells, thus aggravating the pathological process of intervertebral disc degeneration. There are also cytokines in the interleukin family that inhibit intervertebral disc degeneration and play a protective role in the process of intervertebral disc degeneration. The pathological process of intervertebral disc degeneration is very complicated. Interleukin family cytokines have both synergistic and antagonistic effects. Furthermore, related targeted gene interventions have made breakthrough progress. China has made the greatest contribution in this field, and its research interest is naturally the highest. Cooperation among countries is also very important. Moreover, China and the United States, the two countries that have made the most outstanding contributions to this field, have invested a lot of money to help this field, showing a strong development prospect in this field. It is expected that the number of publications in this field will increase in the future, and the expression of interleukin cytokines and the biological effects of cytokines on nucleus pulposus cells will remain our focus in the future. It is not only clinical medicine, but also a comprehensive analysis of this field from the perspectives of biology and immunology is the latest research direction. Similarly, the development of this field also needs the joint efforts of all disciplines to further summarize the interaction mechanism between them, so as to achieve the purpose of precise treatment.

Abbreviations

WOS, Web Science; IF, Impact factor; RRI, Relative research interest; IL(1-38), Interleukin(1-38); NP, Nucleus pulposus; AF, Annulus fibrosus; CEP, Cartilage endplate; Collagen-II, Type II collagen; TNF-α, Tumor necrosis factor-α; CSF, Colony stimulating factor; VEGF, Vascular endothelial growth factor; POGF, Platelet-derived growth factor; MCP, Monocyte chemotactic proteins; MMP, Monocyte chemotactic proteins; ADAMT, Disintegrin and Metalloproteinase with Thrombospondin Motif; PGE2, Prostaglandin E2; HIF-1α, Hypoxia-inducible factor 1α; JAK-STAT, The Janus kinase-signal transducer and activator of transcription pathway; MAPK, Mitogen-activated protein kinase.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Haoran Wang and Xiaoqing Li made the same contribution to the manuscript.

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