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Intelligent structure prediction and visualization analysis of macrophage-mediated immunomodulation in spinal cord injury repair research

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Abstract: Spinal cord injury (SCI) is a devastating global neurological disorder, and immunomodulation is critical to SCI repair. This study aimed to explore the roles of macrophages and immunomodulation in SCI repair, establish a relevant knowledge base, and identify research trends and hotspots. Articles on SCI and related immunomodulation up to November 2024 were retrieved from the Web of Science Core Collection, and bibliometric analyses were performed using bibliometrix, Citespace, VOSviewer and other tools to visualize cooperation networks and quantify authors, countries, institutions, journals and keywords.A total of 894 papers from 49 countries were included, with China being the most productive (315 papers). Ohio State University, Phillip G. Popovich, and Journal of Neuroinflammation were the most influential institution, author and journal respectively. Key hotspots included axonal regeneration and related neuroimmune models. In conclusion, macrophages—particularly the balance between M1 and M2 phenotypes—play a critical role in neural recovery following SCI. While the body of research in this area is growing, enhanced international and inter-institutional collaboration remains essential to advance this field and benefit patients with spinal cord injuries.

1. Introduction

Spinal cord injury (SCI) is a critical medical condition in which the spinal cord's structure or function is disrupted by external factors, disease, or other causes, resulting in problems with motor skills, sensation, and autonomic functions. It is a central nervous system (CNS) disorder, the condition could be caused by both traumatic and non-traumatic factors, leading to spinal cord damage. This injury results in temporary or permanent impairment of movement, sensory, as well as other abilities below the site of the wound, making it a major cause of paralysis[1]. According to a survey,

approximately 900,000 people worldwide experience spinal cord injuries annually and the age-standardized incidence of SCI reached 13/100,000 people[2], In China, incidence and prevalence of SCI reached 2,766,277 and 99,363 cases, respectively[3]. SCI may See new explosive growth as time goes on and the economy grows[4].At the same time, patients with spinal cord injuries suffer from varying degrees of loss of ability to care for themselves after the injury, as well as long treatment and rehabilitation times[5], all of which increase the financial burden on patients and bring economic losses to society. The National Center for Spinal Cord Injury Statistics calculated that a highly quadriplegic patient spends more than $1.06 million in the first year[6]. SCI is prone to symptoms such as ischemia and edema[7], but because the pathogenesis of components after SCI is unclear, the effects of macrophages in the repair of SCI has not been fully clarified either, so this paper aims to analyze the relevant conclusions through bibliometrics, to expand the relevant theories, and to provide ideas for the proposal of effective treatment methods.

An inflammatory response may occur locally after SCI, resulting in increased damage to nerve tissue. This inflammatory response may trigger an increase in neural excitability, which in turn induces spasticity. The etiology of SCI can be categorized into 2 phases: the original damage phase as well as the secondary / persistent damage phase. The original injury leads to irreversible cellular damage and tissue necrosis, whereas sustained damage to spinal cord cells often exhibits revocable regulatory cell death (RCD)[8]. After spinal cord injury, the body's immune system begins to repair itself, a complicated and crucial procedure involving multiple cells and molecules interacting and ultimately plays an important part in the repair of SCI[9]. Studies have shown that macrophages in the central system play a key part in the aftermath of a stroke, with CNS-associated macrophages (CAMs) affecting adherence molecules on endothelial cells, activating them, and thereby orchestrating the migration of immune cells[10]. Modulation of the inflammatory response, modulation of immune cells, and neuroprotection are the main manifestations of immune regulation after SCI[11] . Macrophages are immune cells derived from monocytes, which are differentiated from monocytes. Their mechanism of action is to recognize and phagocytose foreign pathogens in the form of fixed or free cells, thus responding to pathogens, and at the same time, it can activate lymphocytes or other immune cells. Macrophages are divided into two major groups: M1 and M2. Classically activated M1 macrophages secrete proinflammatory cytokines, including IL-1 β and TNF-α, while alternatively activated M2 macrophages have anti-inflammatory and tissue repair functions[12]. They sense and can respond to components of the extracellular matrix (ECM) by producing proteases that contribute to ECM degradation. When tissues are damaged, macrophages can remove damaged cells and their debris and secrete immune-regulating factors, through which they mediate the removal of damaged tissues by immune-regulation-associated cells. In addition, local stromal and precursor cells are stimulated to secrete mediators to repair damaged tissue[13]. Though the association between macrophages and SCI has been published, we need to systematically investigate the effects of macrophages in the repair of SCI, to grasp some hidden connections between them, and to grasp and speculate the most accurate research direction for a brand new exploration. It also provides a new approach to drug therapy based on the functional characteristics of macrophages and a new way of thinking about the treatment of SCI. In this way, we can help spinal cord injury patients repair spinal cord damage and nerve damage.

Bibliometric analysis is an inter-disciplinary study, widely used in different areas of medicine, to quantitatively analyze literature information through mathematics and statistics, to study the linkages between articles, journals, authors, international, institutions, and other factors surrounding a relevant topic, and thus to speculate on the influence, relationships, and trends that develop in each factor[14][15]. A literature review is a summary and generalization of the substance of previous publications within the framework of a predetermined study. Compared with literature reviews, bibliometrics eschews the constraints of literature reviews and Offer a more visual and organized

analysis of publications in a more quantitative form, which is more helpful for researchers to grasp the general tendency of the field. Some literature reviews also explore the mechanisms involved[16], but there are disadvantages in terms of time and mode, to improve the relevant content, this study through the combination of quantitative analysis and qualitative analysis of each other, through the newer data, a better way to determine the effect of macrophages in the repair of SCI after their application and to determine the future direction of macrophage development, and to speculate on the results that can be achieved.

2. Materials and Methods

2.1 Data sources and search strategy

We used The Web of Science Core Collection (WoSCC) to search for relevant English-language publications published between November 2008 and November 2024.The search strategy was as follows: TS= (macrophage* OR "macrophage cell*" OR macrophagocyte* OR "alveolar macrophage" OR "rhagiocrine cell*" OR histiocyte OR megalomania OR megalophages) AND TS= ("spinal cord injury*" OR "myelonic injury*") OR "myelonic injury*" OR "spinal injury" OR "spinal cord injury in rat*" OR "cervical spinal cord injury") AND TS= (immune* OR immunity* OR immunization* OR immuno* OR immunize*). The 894 screened publications were downloaded as "full text records" and "cited references" and saved as "BibTex" and "plain text files", respectively. "BibTex" and "Plain Text File" for further analysis. The specific operation and screening process is shown in Figure 1.

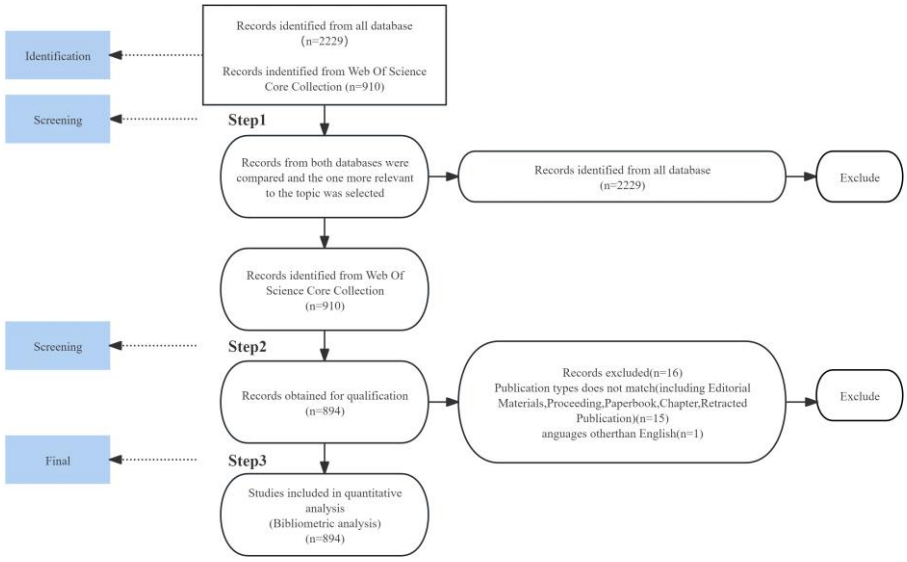


Figure 1 Flowchart of the retrieval and screening process

2.2 Data analysis

For the bibliometric analysis of this study, a total of three tools were used: VOSviewer (version 1.6.20), Bibliometrix (version 4.3.3), and Citespace (version 6.3.R1 BASIC). Bibliometrix is a data visualization tool and a comprehensive mapping and analysis tool that must be used in an R environment to support the bibliometric analysis process of data import and transformation, bibliometric analysis of datasets, and the construction of matrices. Comprehensive bibliometric mapping analysis of articles by journal, author, country, institution, and other factors is performed

through the Biblioshiny application to analyze the association of individual articles in this direction. VOSviewer is a software tool for creating and exploring maps based on network data, which is used for unidirectional and undirected network analysis to construct, view and modify bibliometric maps. It can construct author or journal maps based on co-citation data and keyword maps based on co-occurrence data[17][18]. In this study, we used VOSviewer to display co-occurrence network analysis of authors, issuing countries, and keywords. CiteSpace is a Java-based app that focuses on visualizing and analyzing hot topics and frontiers in the scientific literatures of specific disciplines or areas of knowledge, and it does this in the main way of co-occurrence analysis, cluster analysis, etc[19]. We use Citespace to analyze the connections between individual countries and keywords to explore to discover patterns.

3. Results

3.1 Analyzing the number of published articles

Pubmed collected a number of 907 papers related to macrophage immunomodulation in spinal cord injury repair, which yielded a total of 894 papers after screening, including 793 articles and 145 reviews. During these 17 years, the quantity of relevant papers has increased steadily, with an average annual growth rate of 9.3%.

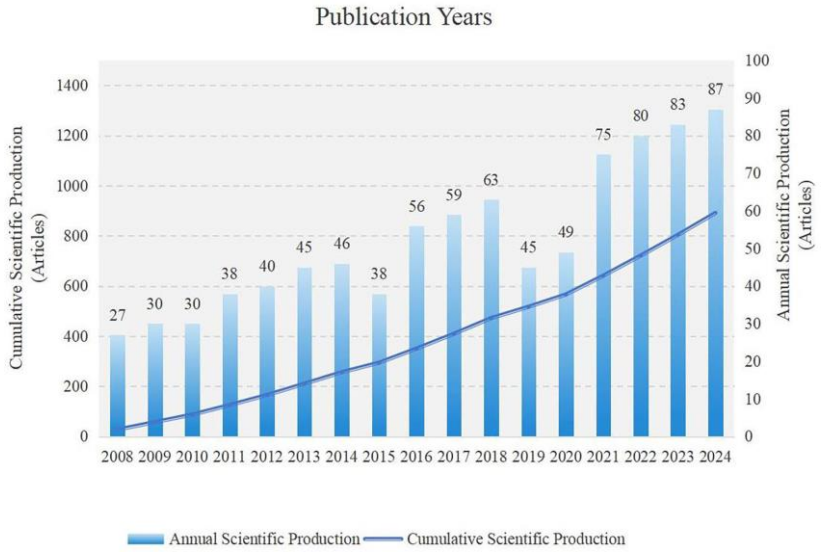


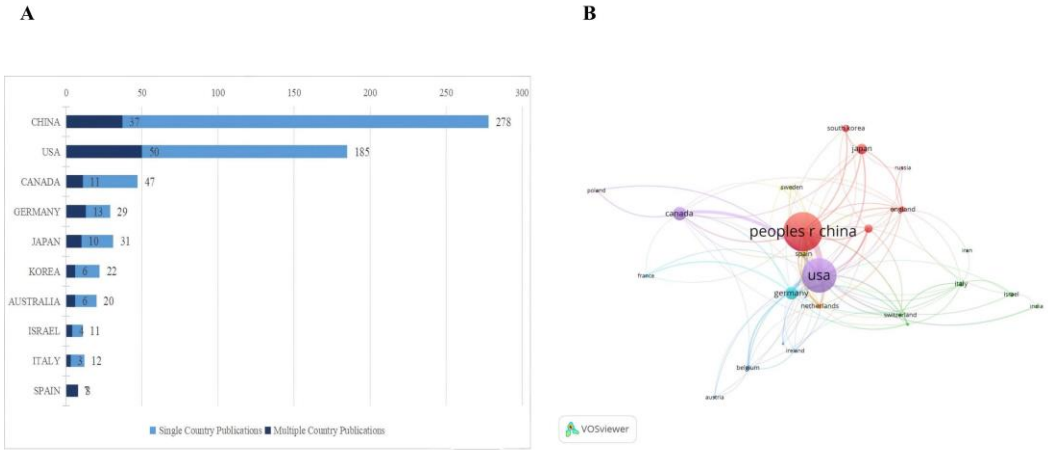
Figure 2 Annual and cumulative scientific production

Analyzed by Figure 2, the average annual number of publications in 2019-2020 is 47, showing a slow growth trend and a low number relative to the previous years. However, in recent years, the average annual publication volume has reached a record high and has shown a gradual growth trend. As of November 2024, the total publications for 2024 reached a record high of 87 titles. The quantity of publications has increased greatly over the last decade, from 294 in 2015 to 891 in 2024, an average of 59.7 publications per year.

3.2 Countries and institutions analyzed

Based on the analysis of the nationality of the corresponding authors, a number of 49 countries were involved in the study of the effects of macrophages in the repair of SCI. China was the country with the largest number of publications, totaling 315 articles (35.23%), followed by the United States with 235 (26.29%) and Canada with 58 (6.48%), and Germany and Japan also had 42 and 41 articles,

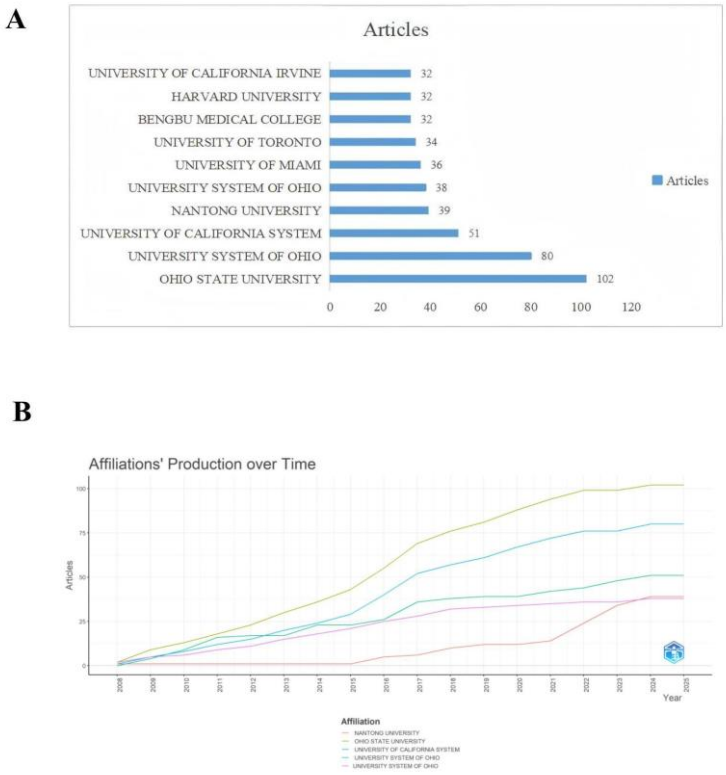
respectively (Figure 3A). Multi-country publications (MCP) are those co-authored by authors of more than one nationality, while single-country publications (SCP) are those co-authored by authors of the same nationality. The United States is the country with the highest number of collaborations, totaling 50 collaborations, accounting for 33.78% of the world's MCPs, and China, although accounting for only 23.45% of the total number of MCPs, is still the most active country in international collaborations, collaborating with 27 countries (Figure 3B). China had the highest number of SCPs with 278 publications. Spain, on the other hand, although ranked 10th in terms of publications, has an extremely high percentage of MCPs, at 70%, indicating active collaboration with various countries and more international exchanges. In this study, the minimum number of citations for citation analysis utilizing Vosviewer was limited to 5, and a number of 25 countries were analyzed. In a VOSviewer setup, each node represents a country, and the thickness of the lines between individual nodes indicates the strength of the connection between them, which is called the Total Link Strength (TLS).The United States ranked first with 15,857 total citations and 68.30 average citations per article, while China also ranked second with 7,123 total citations. It is noteworthy that the average citations per article in Israel are as high as 131.90, indicating that the quality of Israeli articles is relatively good. Over the past five years, China, Australia, Germany, and Spain have emerged as promising countries in the field. Among them, China is the country with the highest momentum and potential due to its increasing number and quality of articles. Meanwhile, according to Figure 4A, the United States accounts for seven of the ten most relevant institutions, while China boasts Bengbu Medical University and Nantong University. Among them, Ohio State University is in the first place with 102 published articles, while Nantong University, with a late start but rapid development of results, has published 39 relevant papers, thus rapidly rising to the third place (Figure 4B).



A: Country distribution of corresponding authors; B: Citation network visualization by countries.

Figure 3 Visualization and analysis of data for relevant countries

Each country represents a node, and node size is directly proportional to the number of citations.

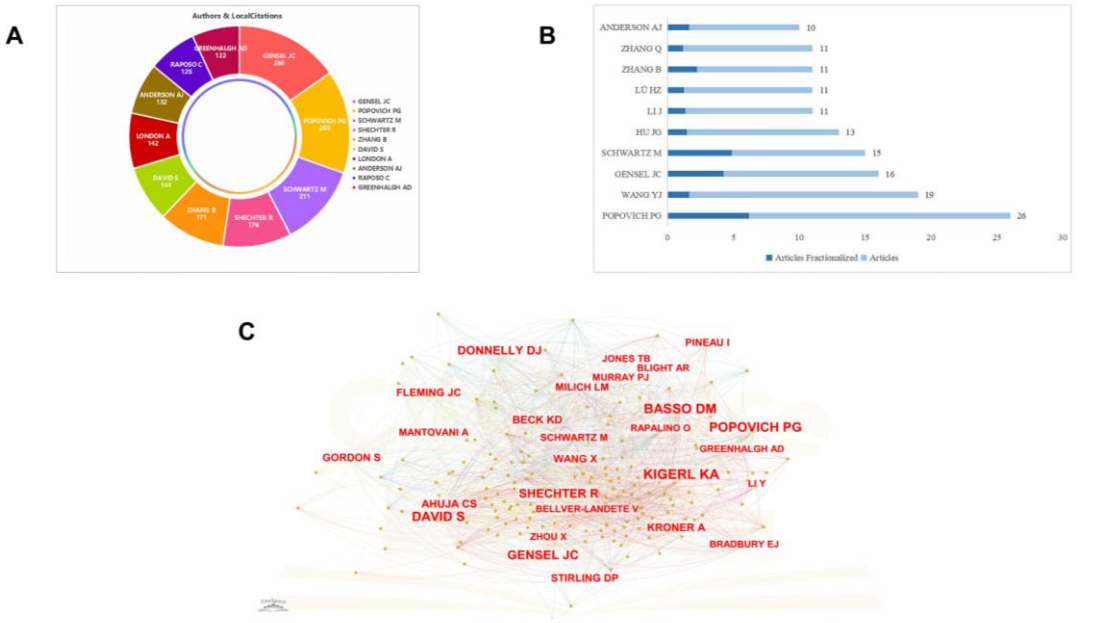


A: The top ten institutions in terms of number of publications; B: Top 5 institutions in terms of production over time

Figure 4 Data visualization and analysis of relevant research institutions

3.3 Analyzing authors

According to the list of papers, after screening by Citespace software to remove duplicates, there are 5093 authors who have written articles related to the effects of macrophages in the repair of SCI. A sum of 37 authors participated in the co-citation analysis, with a citation threshold of no less than 40 citations. Inside the analyzed graph, the highest TLS, number of publications was Popovich PG from Ohio State University (Figure 5B), followed by Kigerl KA from Ohio State University and Donnelly DJ from the University of Maine. Based on the statistical calculations of the data, it was known that Gensel JC from the University of Kentucky had a total of 268 citations in her paper in the first place (Figure 5A), and she also published her paper in highly cited papers in 2015 and 2018 with a total of more than 50 citations per year, which shows that she has a high influence in the field. Popovich of Ohio State University, on the other hand, maintains the quality of his articles while maintaining high productivity, and he is in the second place in terms of the number of citations, while it can be seen that he communicates closely with other authors (Figure 5C) which shows his authority in the field. In summary, It is can be seen that the effect of macrophages in the repair process after SCI has become a hot topic in recent years, and more and more scholars are focusing on the development of this related topic.



A: The top ten authors in terms of total citations; B: Top 10 authors in terms of publications; C: author co-citation analysis visualization network, where each node represents an author and the size of the author's name is proportional to the number of citations received.

Figure 5 Visual analysis of data from relevant published authors

3.4 Analyzing journals

Biblioshiny is a software to be used to analyze bibliometric data, which is carried out in the R language and is mainly used to visualize the analysis of sources, authors, and documents.[20]. As shown in Table 1, there are 894 articles related to repair after SCI,while the most relevant source journals are the Journal of Neuroinflammation, Journal of Neurotrauma, Experimental Neurology, Neural Regeneration Research and Journal Of Neuroscience, of which Journal of Neuroinflammation is a Region 1 journal with an impact factor of 9.3, and 50 articles detailing the effect of macrophages in process of repairing SCI have been cited 3390 times, which has been recognized in the field. 3390 times, which is widely recognized in the field and has a strong influence in the field.

Table 1 Top 10 Most Relevant Periodicals

Sources	Articles	Total Citations	JCR (2023)	IF (2023)	Fields
JOURNAL OF NEUROINFLAMMATION	50	3390	Q1	9.3	Neurosciences; Immunology
JOURNAL OF NEUROTRAUMA	37	2010	Q2	3.9	Neurosciences; Clinical Neurology; Critical Care
EXPERIMENTAL NEUROLOGY	36	1830	Q2	4.6	Neurosciences
NEURAL REGENERATION RESEARCH	21	1236	Q2	5.9	Neurosciences; Cell Biology
JOURNAL OF NEUROSCIENCE	19	1163	Q1	4.4	Neurosciences
BRAIN BEHAVIOR AND IMMUNITY	15	1161	Q2	8.8	Neurosciences;Immunology; Psychiatry
FRONTIERS IN CELLULAR NEUROSCIENCE	15	1146	Q3	4.2	Neurosciences
GLIA	15	983	Q2	5.4	Neurosciences
MOLECULAR NEUROBIOLOGY	14	834	Q2	4.6	Neurosciences; Molecular Neurobiology
SCIENTIFIC REPORTS	14	782	Q2	3.8	Multidisciplinary Science

3.5 Analyzing research hotspots

3.5.1 Analyzing Literature Citation Outbreaks

The analysis of citation explosion is considered to be the key to tracking and capturing hotspots, and its mechanism is to analyze the literature with citation peaks, so as to clearly reflect where the hotspots are[21]. As shown in Figure 6, "The cellular inflammatory response in human spinal cords after injury" published in Brain in 2006 has the earliest burst value: 9.68, and this burst value lasted from 2008 to 2008. Burst values lasted from 2008 to 2011. The highest Burst value is from 2009 "Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cords", which has the earliest Burst value: 9.68, and this Burst value from 2008 to 2011. In addition, several articles, such as "Macrophage phagocytosis after spinal cord injury: when friends become foes", have gradually shown that macrophages engage in phagocytosis after spinal cord injury, leading to immune suppression. In addition, several articles, such as "Macrophage phagocytosis after spinal cord injury: when friends become foes", have gradually shown that macrophages phagocytose after spinal cord injury, leading to immune suppression. The trend of these articles suggests that this type of research on the role of macrophages in the repair process after spinal cord injury may still be at the forefront[22].

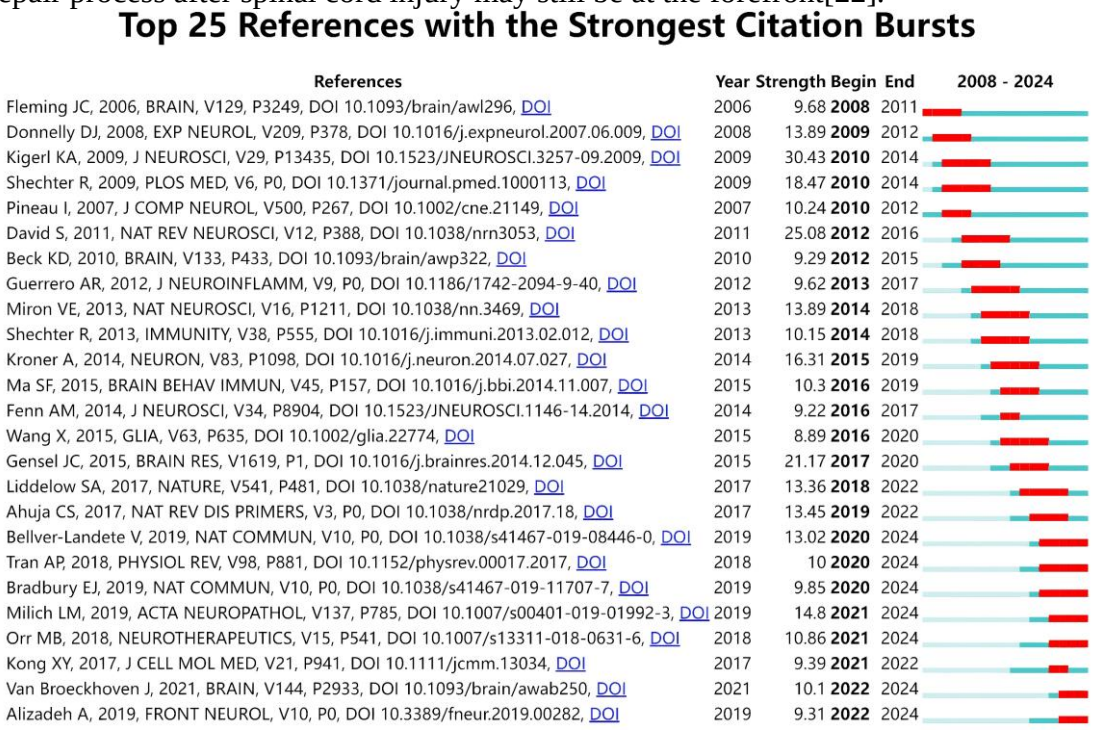


Figure 6 The top 25 most references with the strongest citation bursts.

The light green lines segment represents the time period before the article was published, the dark green line segment represents the time period after the article was published, and the red line segment represents the duration of the article's citation burst.

3.5.2 Standardized total citations and total citation frequency analysis

Standardized total citation count and total citation frequency are two standard citation analysis tools widely used to reflect academic impact. Nowadays, citation analysis is an important tool for performance evaluation of medical science research. Nevertheless, the value of the indicators of citation analysis varies in different fields[23], so it is difficult to make comparisons, while even within

the same medical field, there may be considerable differences between different areas of medical research. Therefore, the standardized total number of citations is particularly rare and important as an indicator that can more fairly reflect the academic impact of articles. As shown in Table 2, the article "Infiltrating Blood-Derived Macrophages Are Vital Cells Playing an Anti-inflammatory Role in Recovery from Spinal Cord Injury in Mice" was published in 2009 and placed first in the list of standardized citations, which shows that this article has a high degree of recognition and influence in the field. Among the top ten articles, all of them have more than 450 citations, and they are all related to the link between SCI and macrophages. The article “Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury”, published in 2008, is the most popular article in the field, and at the same time, it is the most cited, with 757 citations (average 44.53 citations per year). We also need to analyze the total citation frequency to prevent the difference in publication year from affecting the determination of article quality. In terms of total citation frequency, the article "Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms” published in 2020 had an annual average of 112 citations.“ won the first place with an average of 112.4 times per year, although his total number of citations is not high, through the analysis of the total citation frequency can be seen that it is a highly influential article.

Table 2 Top 10 articles in total citations.

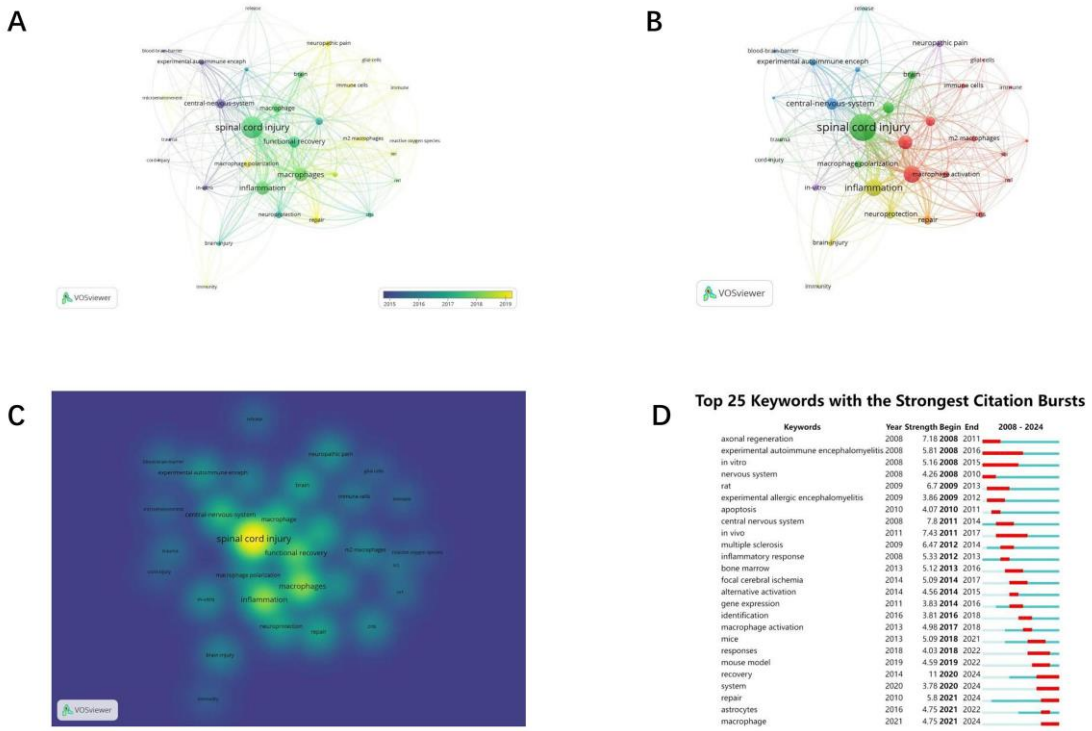
Rank	Title	Journal	Year	Total Citations	Total Citations per Year	Normalized Total Citations
1	Inflammation and its role in neuroprotection, axonal regeneration, and functional recovery after spinal cord injury	EXP NEUROL	2008	757	44.53	9.36
2	Macrophage polarization: An opportunity for improved outcomes in biomaterials and regenerative medicine	BIOMATERIALS	2012	698	53.69	9.19
3	Cell transplantation therapy for spinal cord injury	NAT NEUROSCI	2017	612	76.5	10.68
4	Infiltrating Blood-Derived Macrophages Are Vital Cells Playing an Anti-inflammatory Role in Recovery from Spinal Cord Injury in Mice	PLOS MED	2009	603	37.69	6.01
5	Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms	INT J MOL SCI	2020	562	112.4	10.72
6	Macrophage activation and its role in repair and pathology after spinal cord injury	BRAIN RES	2015	535	53.5	8.12
7	Role of Microglia in Neurotrauma	NEUROTHERAPEUTICS	2010	497	33.13	6.32
8	Microglia in the TBI brain: The good, the bad, and the dysregulated	EXP NEUROL	2016	490	54.44	7.88
9	TNF and Increased Intracellular Iron Alter Macrophage Polarization to a Detrimental M1 Phenotype in the Injured Spinal Cord	NEURON	2014	482	43.82	5.87
10	Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment	BRAIN	2010	475	31.67	6.04

3.5.3 Analyzing Keywords Co-occurring Network

The co-occurrence network analysis of the keywords mainly shows the major directions and themes of the research through the frequency of key words and the number of co-occurrences, and can summarize the hot spots of related research. In this study, Citespace and VOSviewer, respectively, were used to better reflect research trends on keywords and related topics. On Citespace, after a threshold of no less than 25 occurrences, a total of 21 met the criteria, “spinal cord” “central nervous system”, “regeneration”, and “macrophages” were the most closely associated with other keywords (Figure 7A). However, the present study excluded the keywords “spinal cord” and “macrophages” because the search topic of this study conflicted with them. On Vosviewer, after a threshold of no less than 5 occurrences, a total of 372 keywords were screened out of 3902 keywords that met the

criteria according to the popularity of the time, and in Figure 7C, different keywords were divided into clusters with different colors. Among them, the dark blue keywords “central-nervous-system”, “experimental autoimmune enceph", and "blood-brain barrier" represents the early research themes. In yellow, "m2 macrophages", "immune cells", "repair", and "neuropathic pain" represent the early research themes. "Neuropathic pain" in yellow represents the hot topics in recent times, which can be used as a preliminary indicator of the direction of recent research. Around the term "spinal cord injury", it can be found that it is closely associated with many keywords, such as "functional recovery", macrophages" and so on. In addition, the term "macrophages activation" is widely associated with keywords such as "m2 macrophages" and "spinal cord injury". In addition, "macrophages activation" is also widely associated with keywords such as "m2 macrophages" and "spinal cord injury" (Figure 7B), which have received great attention and provided a new idea for subsequent research directions. It can be explored from the perspective of macrophage activation. The citation outbreak analysis of keywords can accurately and intuitively show the trend of a research hotspot and its changes, and provide directions for subsequent research in the field.[24]. In this study, we explored the top 25 intensities of highly cited outbreak keywords (Figure 7D). Among them, “axonal regeneration” (intensity: 7.18), “experimental autoimmune encephalomyelitis” (intensity: 5.81) ,“in vitro” (intensity: 5.16) and “nervous system” (intensity: 4.26) are the earliest highly cited outbreak keywords in the past 17 years. The highest intensity outbreak word is “recovery” (intensity: 11). In the last 5 years, “system” (intensity: 3.78), “repair” (intensity: 5.8), and “recovery” (intensity: 11) are the most highly cited outbreak keywords, which are all consistent with the co-occurrence results of the keywords. Therefore, it can be analyzed that the current research in this field is consistent with this study.

It is worth noting that M1-type macrophages and M2-type macrophages also occupy an important position among the keywords, with M2-type macrophages appearing a total of 34 times, whereas M1-type macrophages appeared 12 times, and these two keywords are also very closely related to other keywords, with the TLS value of M1-type macrophages being 138, whereas the M2-type was as high as 318, which are all indicators suggesting an important role of M1-type macrophages and M2 Macrophages are important immunomodulators in the repair of SCI. In the temporal visualization of the keywords, “M2 Macrophages” was in the yellow cluster representing the latest topics (Figure 7C), which indicates that the current research hotspot is gradually approaching the study of the mechanism of action of specific types of macrophages.



A: Keyword co-occurrence analysis overlay visualization; B: Keyword co-occurrence analysis network visualization; C: Visual analysis of keyword co-occurrence density; D: The top 25 keywords with the strongest citation bursts. The light green line segment indicates before the keyword appears, the dark green line segment indicates after the keyword appears, and the red line segment is the duration of the keyword citation burst.

Figure 7 Analysis of keyword co-occurrence network

3.5.4 Analyzing the number and frequency of citations

In the academic field, the quantity and quality of results on a topic are important indicators of how well the topic has developed, and quality is often expressed in terms of the number and frequency of citations.[25]. There has been a general upward trend in the quantity of publications on this topic over the past decade or so, and a new peak has been reached in recent years. However, although the quantity of publications has increased, the number of average citations per year has declined, which is related not only to a decrease in citations due to the newer age, but also to a decrease in the quality of the articles themselves. The overall publication level still needs to be further improved.

4. Discussion

4.1 Global Research Trends on the Immunomodulatory Role of Macrophages in the Repair of Spinal Cord Injury

A country's medical research output depends largely on its economy and healthcare expenditures, in addition to being determined by scientific research funding. According to the data released by China's National Health and Wellness Commission 2024, China's healthcare expenditure in 2023 will be about 90,575.8 trillion RMB[26] (about 12,473.1 trillion USD). With a growth rate of 5.5%, which shows that China's rapid development in the field of medical research can not be separated from the growth of its healthcare expenditure. According to data released by the Statista Research Department in 2024, the U.S. ranked first in the world in healthcare spending, with more than $4.4 trillion[27].

This may explain why China is growing rapidly in this field, while the United States maintains its lead in the total number of citations and international collaborations.

Inter-country and inter-agency cooperation can help reflect the level of activity and development in the field. The cooperation between countries can help to fill in the shortcomings of each country, which can help to further develop the scientific research activities rapidly. A large portion of the articles in Figure 3A are done by various countries in collaboration (MCP), such as the United States, China, Germany, and Canada, all of which have extensive collaboration with various countries. In turn, the number of articles from institutions and the number of collaborations with each other can reflect the level of activity in the research discipline. As shown in Table 3, Ohio State University in the United States is the leader in this field and maintains a leadership position in terms of both the quantity of collaborations and the number of articles in the development process, which also boasts well-known scholars such as Popovich, PG. Nantong University from China, on the other hand, is a latecomer to the field and has achieved rapid growth in just five years, publishing 25 papers in just four years. It has been shown that Nantong University has a key laboratory, the Institute of Neural Regeneration, which has ushered in rapid progress in the last few years with the establishment of its alumni association and the addition of academicians to the organization, so it is evident that Nantong University's has grown in the field for a reason. Thus, it shows that institutions are one of the foundations for the development of subject areas, and the development of high-level institutions can ensure and drive the rapid development of academic research.

At the same time, journals are also an important indicator of the topic, and the quality and topics of the journals can reflect the heat and trend of the topic. As shown in Table 1, nine of the top ten journals are in Region II and above. Nine journals are about neuroscience and one is about multidisciplinary science, which shows that the relevance of the topic is strong. Meanwhile, the impact factors of the ten journals are also very high, which shows that the journals are highly influential and highly referenced. The first one is JOURNAL OF NEUROINFLAMMATION, which has published 50 articles related to the topic and has been cited 3390 times[28], which is one of the most influential journals. It mainly deals with central nervous system inflammation[29], spinal cord injury[30], spinal cord injury repair[31].

In terms of authorship, GENSEL JC of the University of Kentucky is one of the authors who remain competitive in this field, as shown in Figure 5A, she ranked the first place with a total of 268 citations, and her article "GENSEL JC, 2015, BRAIN RES" was also ranked the sixth place in the article, which shows that her article is of high quality and high impact. This shows that her articles are of high quality and high impact. Her discussion on the physiology and pathology of spinal cord repair after spinal cord injury is very informative[32].

4.2 Prediction of hot spots and research development

The prediction about the development of hotspots and research trends cannot be separated from the reflection of keywords, article citation counts, and other indicators. The investigation and study of keywords and citation counts, can help us to obtain the latest research trends and capture the new research development direction. Through the R software package "bibliometrix", we can conclude that the words “spinal cord injury”, “macrophage”, “activation” and such keywords are the most frequently appearing words. The frequency of the words “spinal cord injury”, “macrophage” and “functional repair” has increased rapidly over time. However, because “spinal cord injury” and “macrophage” overlapped with the topics searched for, this study only explored keywords other than these two. The high frequency of the words "activation" and "functional repair" suggests the possibility of this direction of development, as shown in Table 3 for "functional repair" in the context of immunomodulation. As shown in Table 3, the words "inflammation" and "activation" in the context

of immunomodulation are growing rapidly, and these hot topics may signal further changes in the way the field is researched in the future, with "activation" and "functional repair" being the most common. These hot topics may signal further changes in the way the field is researched in the future, with terms such as “activation” and “functional repair”. This is also closely related to the present study on the role of macrophages in the repair process of spinal cord injury. In addition to the duplicates of the search terms, the keyword "activation" was most closely associated with other terms, as shown in Figure 7B, where "spinal cord injury" was associated with "functional repair", and "functional repair" was associated with "spinal cord injury" and "functional repair". As shown in Figure 7B, "spinal cord injury" is most closely related to "functional repair" and "central nervous system", which suggests that the brain in the CNS undergoes some degree of spontaneous functional recovery first after SCI[33]. The relationship between spinal cord injury and stem cells is also shown in Figure 7B. In related research, a review has shown the feasibility of stem cell therapy in the process of spinal cord injury repair[34], and macrophages are differentiated from hematopoietic stem cells[35], and the relationship between the two provides unlimited opportunities for imagination about the role of macrophages in the future repair of spinal cord injury. Meanwhile, as shown in Figure 7C, “macrophage” is closely related to the keywords “activation”, “regeneration” and “inflammation”. As shown in Figure 7C, “macrophage” is closely related to “activation,” “regeneration,” and “inflammation,” which also provides a good idea to explain the effects of macrophages in the recovery process after SCI.

Table 3 Top 8 keywords in terms of frequency of occurrence and their trends over time

Year	Spinal-Cord-Injury	Macrophages	Activation	Functional Recovery	Expression	Regeneration	Central-Nervous-System	Inflammation
2024	258	167	164	164	146	138	122	119
2023	239	144	147	156	134	122	120	108
2022	226	126	126	139	119	112	119	93
2021	214	116	106	123	103	97	115	76
2020	196	103	88	113	95	87	111	63
2019	184	95	76	106	90	76	108	56
2018	177	85	61	97	78	70	104	48
2017	158	73	44	81	65	58	94	37
2016	135	64	35	66	55	48	80	33
2015	111	55	29	54	46	38	70	29
2014	96	48	24	45	36	32	63	24
2013	78	37	18	42	31	27	52	18
2012	61	27	13	35	23	19	39	13
2011	45	22	9	29	18	10	29	10
2010	37	16	5	18	13	5	21	5
2009	26	9	3	9	9	3	19	3
2008	14	5	2	4	3	1	11	1

4.3 The role of macrophages in the repair of SCI and its mechanism.

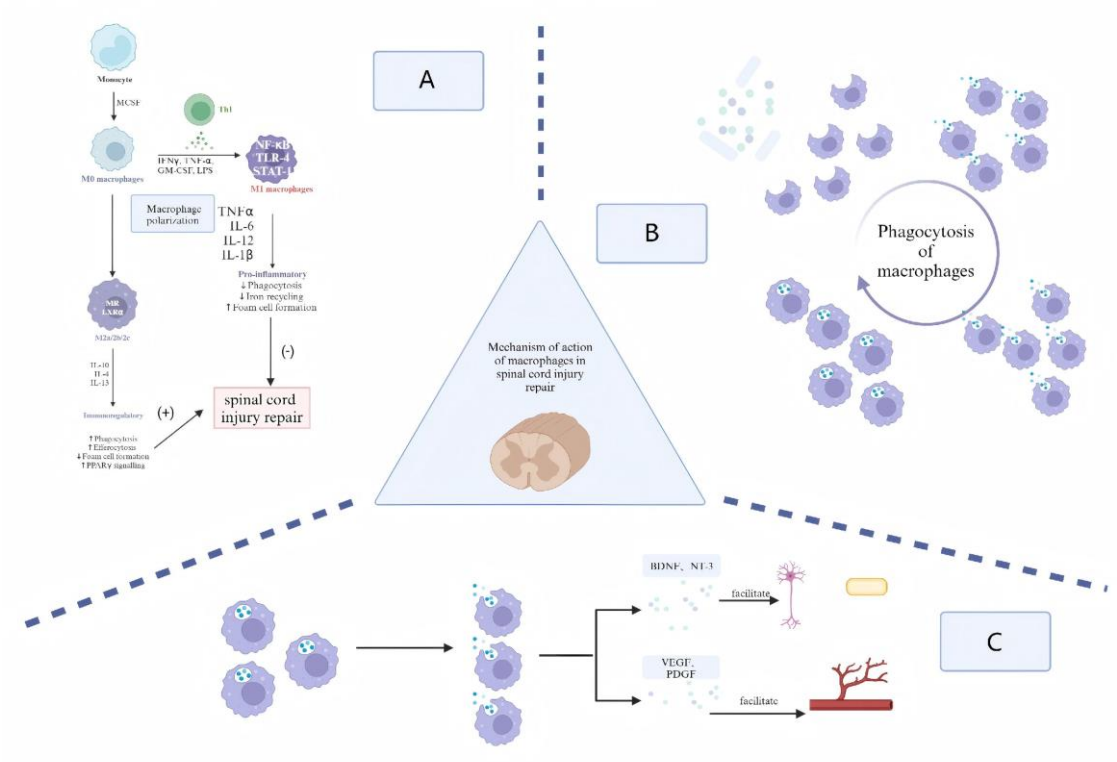
Macrophages have an important effect after SCI. Meanwhile, with the development of related medical research, more and more researchers will notice the important role played by macrophages.

4.3.1 Macrophages can regulate information pathways through polarization and maintain the balance of inflammatory dynamics to achieve functional repair (Figure 8A)

It is increasingly recognized that neuroinflammation is a major driver of CNS pathology[36]. Thus the regulation of neuroinflammatory responses plays an important role in spinal cord injury repair. Macrophages can be polarized into M1 and M2 types after spinal cord injury[37] (Figure 9), where M1 types have pro-inflammatory effects, promoting inflammation and exacerbating tissue damage by secreting pro-inflammatory factors (e.g, TNF-α, IL-1β)[38]. M2 type can release anti-

inflammatory factors (e.g, IL-4, IL-10) to inhibit inflammation and promote repair[39]. Meanwhile, the M1 type can be repolarized and transformed with the M2 type to inhibit or promote inflammatory diseases[40], and through the bidirectional regulation of two types of macrophages to regulate the information pathway, modulates inflammation and stimulates repair of injured spinal cord.

The nomenclature of M1 and M2 derives from the pro- or anti-imflammatory activation of macrophages in vitro, and there are remarkable differences between the two in terms of activation markers, receptors, cytokine secretion and so on. In the process of spinal cord injury repair, M2 macrophages can inhibit the NF-KB pathway by releasing IL-4 and IL-10, thus reducing the release of pro-inflammatory factors, and in addition, through the reducing the level of pro-inflammatory factors, they inhibit the inflammatory overreaction, thus maintaining the dynamic balance of the inflammatory response. Macrophages are therefore key to the success of the inflammatory response by relying on their ability to rebalance the pro-inflammatory and pro-ablative responses[41]. It has a cardinal function in the mediation of the inflammatory response to SCI repair.



A: Macrophages achieve functional repair through polarization; B: Macrophages reduce phagocytosis of secondary injury; C: Macrophages promote regeneration of spinal cord structures

Figure 8 Schematic representation of macrophage immunomodulation after SCI based on this study, which was generated by BioRender.com

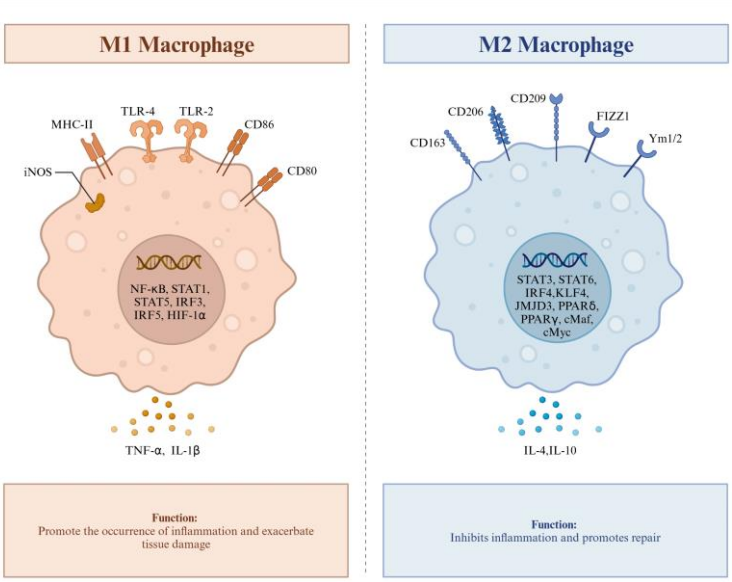


Figure 9 Schematic representation of the mechanism of action of M1-type and M2-type macrophages based on this study, which was derived from Biorender.com.

4.3.2 Macrophages Reduce Secondary Injury by Phagocytizing Injury Debris (Figure 8B)

Macrophages reduce secondary injury by removing necrotic tissue, myelin debris, and cellular debris through phagocytosis.

Following SCI, tissue repair requires the mobilization of immune cells and neuroglial cells to form a protective barrier that seals the wound and facilitates debris removal, inflammation containment, and matrix compression, resulting in accelerated compression and repair of the injured area. This requires the formation of a fenestrated structure, which is made possible by a substance called Plexin-B2[42], which is widely found in macrophages and is therefore essential for the formation of fenestrated structures.

Pro-inflammatory M1 macrophages can phagocytize cells and destroy debris, whereas M2 macrophages can anti inflammatory, like tumor associated macrophages (TAMs), can contribute to the growth and invasion of tumors and other material[43]. Therefore, the control of macrophage phagocytosis can be achieved by regulating macrophage differentiation. At the same time, there is a CD47-SIRPα pathway that regulates macrophage phagocytosis, and blocking this pathway can enhance macrophage clearance of myelin debris and promote repair[44].

4.3.3 Macrophages can promote regeneration of spinal cord structures (Figure 8C)

M2 macrophages can secrete neurotrophic factors (e.g, BDNF, NT-3), thereby directly promoting axonal regeneration and myelin formation[45]. At the same time, it can also inhibit scar hyperplasia by regulating the activation of astrocytes, thus providing a material basis for the repair of the damaged spinal cord and promoting the regeneration of nerves and bones.

Macrophages provide a regulatory basis for vascular regeneration as well. It promotes neovascularization and improves local ischemia by secreting factors such as VEGF and PDGF. It reduces the ischemic death of neurons by alleviating microcirculatory disturbances. Thus modulation of macrophage polarization from a pro-inflammatory phenotype to an anti-inflammatory state is considered a potential curative approach for the treatment of ischemic stroke[46]. Similarly, repair of SCI can be achieved by macrophage regulation during ischemia following SCI.

4.4 Advantages and limitations

This bibliometric study examines the single topic “Function of Macrophages during SCI”in detail and discusses its basic facts, global trends and research hotspots. A more intuitive and adequate immune regulation after SCI can be found through the visual perspective. The result of the research is accurate and objective, which can provide a comprehensive guidance for scholars who have or will carry out related work. Despite this, there are still limitations in this study, firstly, the scope of the search library does not include all, and has not yet searched the non-English databases, and with the development of bibliometrics, it will certainly be further improved to the non-English databases in the future. Secondly, in this study, the research time is mainly focused on the period from 2008 to 2024, and in the future, it may be appropriate to carry out the research in newer or earlier years. Thirdly, it may be that the mechanism of action of macrophages has not been studied in detail and requires further research and improvement.

5. Conclusion.

This study investigated the immunomodulation of macrophages during post-SCI repair from 2008 to 2024 utilizing bibliometric analysis. This study has the advantage of being more visual than review articles, and by examining the countries, institutions, authors, journals, popular keywords, and references related to the topic of this study, we can identify the importance of these factors for the development of the field. Our study focuses on analyzing the research related to the role of macrophages in the repair process of spinal cord injury from 2008-2024 and discusses the relevant principles of macrophage effects and ultimately provides relevant ideas for the future treatment of SCI. Through the study, it can be intuitively found that the research on the role of macrophages in the repair process after spinal cord injury is rapidly developing, in which the M1 and M2 types of macrophages have not been used as an important predictor of the present study, which will have an important developmental value. Further in-depth studies on the mechanisms of M1 and M2 macrophages will provide researchers with different ideas and gradually develop into one of the important directions for the future development of this field, and countries, institutions and individuals should better integrate resources and cooperate to promote the continuation of the research.

6. Data availability statement

If relevant original material is required, please contact the corresponding author(s)

Author contributions

CZ: Data curation, Formal Analysis, Methodology, Software, Visualization, Writing-original draft. HL: Software, Software. LL: Funding acquisition, Resources, Writing – review & editing ZL: Supervision, Formal analysis, Writing – review & editing.

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Conflict of interest

The authors declare that the study was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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