Global trends on exosomes in spinal cord injury: A bibliometric analysis and mini-review

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ABSTRACT

Spinal cord injury (SCI) is recognised as a debilitating condition that often leads to considerable disability and functional limitations. Exosomes, which can be derived from various cell types including bone marrow mesenchymal stem cells, adipose-derived stem cells, dental pulp stem cells, and macrophages, play a pivotal role in the post-SCI landscape. Collectively, it has been observed that these exosomes can modulate the immune response following SCI, regulate the inflammatory environment, inhibit secondary tissue damage, and support neuronal survival and axonal regrowth. However, it is noted that exosomes from different sources exhibit distinct characteristics. Therefore, it is deemed essential to gain a comprehensive understanding of the current knowledge and research directions regarding exosomes in SCI to foster the development of effective therapeutic interventions. In this bibliometric analysis, we conducted to search retrieve pertinent articles from the Web of Science Core Collection and identify pivotal publications, authors, institutions, countries, and keywords that have contributed significantly to the field. This bibliometric analysis offers a thorough examination of the present knowledge landscape and prevailing research trends pertaining to exosomes in the context of SCI. It acts as a valuable asset, catering not only to researchers but also to clinicians and policymakers engaged in research on SCI and therapeutic advancement. Ultimately, this knowledge mapping can advance our understanding of exosome biology and pave the way for innovative interventions to improve outcomes for individuals affected by SCI.

Keywords:
bibliometric analysis; dental pulp stem cells; exosomes; extracellular vesicle; spinal cord injury

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1. Introduction

Spinal cord injury (SCI) is identified as a profoundly debilitating condition characterised by damage to the spinal cord, leading to a spectrum of motor, sensory, and autonomic impairments.[1] The restricted regenerative potential of the adult spinal cord presents a formidable obstacle in the pursuit of achieving functional recovery subsequent to SCI. Therefore, exploring innovative therapeutic strategies is deemed crucial in promoting neurological restoration and improving the quality of life for individuals with SCI.

Recently, the investigation into the therapeutic potential of exosomes within the context of SCI has been accorded significant attention.[2] Exosomes, small extracellular vesicles secreted by nearly all cell types and originating from endosomes, play a central role in facilitating cell-to-cell communication. These minute vesicles are crucial for transporting a wide range of bioactive molecules, including proteins, lipids, nucleic acids, and signalling molecules. They can be internalised by recipient cells and modulate their functional behaviours, rendering exosomes an attractive candidate for cell-free therapy in SCI.

Exosomes derived from a variety of cell sources, such as mesenchymal stem cells (MSCs), neural stem/progenitor cells, and other cell types, have been shown to hold significant promise in mitigating impairments resulting from SCI. Exosomes derived from MSCs, in particular, have been thoroughly examined due to their potential

immunomodulatory, anti-inflammatory, and neuroprotective properties. These exosomes are capable of modifying the immune response following SCI, regulating the inflammatory milieu, inhibiting secondary tissue damage, and promoting neuronal survival and axonal regrowth.[2]

Furthermore, exosomes derived from neural stem/progenitor cells have been reported to have significant potential in promoting neural repair and functional recovery following SCI. It has been documented that exosomes derived from neural stem/progenitor cells enhance neurogenesis, angiogenesis, and remyelination,[3] which are critical processes for spinal cord regeneration. These exosomes can provide a regenerative microenvironment by delivering growth factors, neurotrophic factors, and microRNAs that promote neuronal survival and axonal growth. Moreover, exosomes derived from various cellular sources, such as Schwann cells and endothelial cells, have been shown to exhibit promising therapeutic effects in SCI treatment. Exosomes derived from Schwann cells are capable of promoting axonal regeneration by providing growth-promoting factors and facilitating remyelination. Meanwhile, exosomes derived from endothelial cells have demonstrated angiogenic properties, that promote blood vessel formation in the injured spinal cord, contributing to tissue regeneration and functional rehabilitation.

In addition to their therapeutic potential, exosomes offer several advantages as a delivery system for SCI treatment. They possess inherent biocompatibility, low immunogenicity, and the ability to cross biological barriers, including the blood-brain barrier. These features render exosomes an ideal candidate for targeted drug delivery and minimise potential side effects.

In conclusion, exosomes emerge as promising therapeutic agents for SCI due to their beneficial effects on inflammation modulation, neuroprotection, neurogenesis, angiogenesis, and remyelination. The ability of exosomes to transfer bioactive molecules and regulate recipient cell behaviour underscores their potential as cell-free therapeutic agents for SCI. Nonetheless, additional investigation is required to comprehend the mechanisms of action, optimise exosome production, and address challenges associated with large-scale production and clinical translation. By harnessing the regenerative properties of exosomes, new breakthroughs in the management and treatment of SCI may be achieved, offering hope for functional recovery and an improved quality of life for individuals affected by this debilitating condition.

Understanding the landscape of research on exosomes in the context of SCI is indispensable for identifying trends, knowledge gaps, and future research directions. Bibliometric analysis, a powerful tool for quantitative assessment of scientific publications and their impact, can provide valuable insights into the growth and development of this field. This article aims to provide a comprehensive bibliometric analysis of the research on exosomes in the context of SCI. By systematically evaluating the literature, the aim is to map the knowledge landscape, identify influential publications and authors, and uncover emerging trends. Additionally, a concise mini-review of the significant findings and developments in this field will be provided, shedding light on the potential therapeutic applications of exosomes in SCI management.

Through this interdisciplinary exploration, the hope is to contribute to the collective understanding of the significance of exosomes in SCI and inspire further research that may ultimately lead to innovative treatments and improved outcomes for individuals affected by this debilitating condition.

2. Methods

2.1. Data screening and collection

Bibliometric analysis was conducted using the Web of Science Core Collection database, a widely employed resource for this purpose. Literature data were collected and retrieved from Web of Science Core Collection on June 18, 2023, covering the period from January 1, 2015, to June 18, 2023. The search employed specific terms, including "extracellular vesicle", "exosomes", "spinal cord injury", and "spinal cord injuries", focusing primarily on articles and reviews, exclusively considering English-language literature. To ensure relevance, two authors individually assessed search results, eliminating papers unrelated to exosomes and SCI based on titles, abstracts, and full texts. In instances of differing opinions, an experienced corresponding author assessed the documents. The literature data was exported in a plain text format, including "full record and cited references", and was then downloaded.

Using both CiteSpace 6.1.R6 (developed by Chaomei Chen, Drexel University, USA) and VOSviewer 1.6.18 (developed by Nees Jan van Eck and Ludo Waltman, Centre for Science and Technology Studies, Leiden University, Netherlands), the literature data were analysed through bibliometric techniques. In addition, the annual production of publications centered on exosomes and SCI was graphed using GraphPad Prism (v9.5.0; GraphPad Software, Boston, MA, USA, www.graphpad.com). To create visual bibliometric maps, utilizing VOSviewer, an open-source Java application created by Van Eck and Walterman, various easily understandable visualisations, such as network, overlay, and density representations, were utilised. Within VOSviewer, networks for co-authorship among nations, organisations, and authors were established, overlay visualization maps for source references were generated, density maps for the analysis of author co-authorship within citations were crafted, and co-occurrence analysis on all keywords was conducted. Figure 1 illustrates the data analysis flowchart.

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3. Results

3.1. Publication results and trends

In accordance with the search strategy, a selection of 222 papers investigating the correlation between exosomes and SCI was curated for bibliometric analysis, covering the period from 2015 to June 18, 2023. Figure 2 visually depicts the annual publication frequency on this topic. Over these years, a consistent upward trend in the number of publications is evident, with a notable jump from one paper in 2015 to 62 papers in 2021. Figure 2 highlights the substantial growth, emphasising the increasing interest in investigating the relationship between exosomes and SCI over the last nine years.

3.2. Countries and organisations

In this field, contributions were observed from 24 different countries and involved collaborations with 290 different organisations. China was distinguished by the most substantial output, contributing 174 papers, which accounted for 78.38% of all published works. Following China, the United States contributed 22 papers, constituting 9.91% of the total, whereas Iran, South Korea, and Australia each provided 6 papers, accounting for 2.7% each. Nonetheless, within the top ten nations, publications from Germany exhibited a comparatively lower average citation rate, with an average of 14.00 citations per paper. Iran and India did not have a high average citation rate. Conversely, Austria claimed the top position with the highest average citation rate of 51.50 citations, followed by Poland with 45.67 citations, the United Kingdom with 40.67 citations, the United States with 34.64 citations, South Korea with 25.33 citations, Japan with 23.75 citations, and China with 23.69 citations. (Table 1).

The evaluation of international cooperation involved examining countries'collaboration networks, with inclusion criteria requiring countries to have cooperated with at least two other nations (Figure 3A). Among the 12 nations identified, China took the lead in extensive collaboration by engaging with 14 countries (Figure 3B). Following China were the United States with collaborations involving 11 countries, Germany with 6, Australia with 4, and Iran with 3.

Regarding the top 10 actively participating institutions, their ranking was determined by the number of publications, collectively accounting for 45.95% (102 out of 222) of the total publications, with publication counts ranging from 7 to 18 (Table 2). Remarkably, all the organisations in the top ten list are from China. Nanjing Medical University secured the top position with the highest number of papers (18, 8.1%) and garnered 842 citations. Central South University followed closely with 16 papers (7.2%) and 229 citations, while Zhejiang University contributed 14 papers (6.3%) and received 407 citations. Notably, Nanjing Medical University, which published the most papers (18) on exosomes and SCI between 2015 and 2023, also attained the highest average citation rate (46.78 citations; Figure 3C, D and Table 2).

3.3. Journals and co-cited journals

During the period from 2015 to 2023, 222 papers discussing exosomes and SCI were distributed across 122 academic journals. The top 12 journals, as shown in Table 3, collectively accounted for 30.2% of all publications. The top journal was "Stem Cell Research & Therapy" with nine papers (4.05% of the total), followed by "Journal of Nanobiotechnology" with seven papers (3.15%), "Journal of Neurotrauma" with six papers (2.70%), "Frontiers in Cell and Developmental Biology" with six papers (2.70%), "Neurochemical Research" with six papers (2.70%), and "Molecular Neurobiology" also with six papers (2.70%) (Figure 4A).

Regarding total citations, "Journal of Neurotrauma" led with 346 citations, followed by "Cell Death & Disease" with 253 citations, and "Frontiers in Neuroscience" with 240 citations. Among the top 12 journals, 10 out of 12, or 83.33%, had an impact factor (IF) higher than 5. An overview of journals with at least two publications is presented in Figure 4B, illustrating the prominence and influence of these publications within the field.

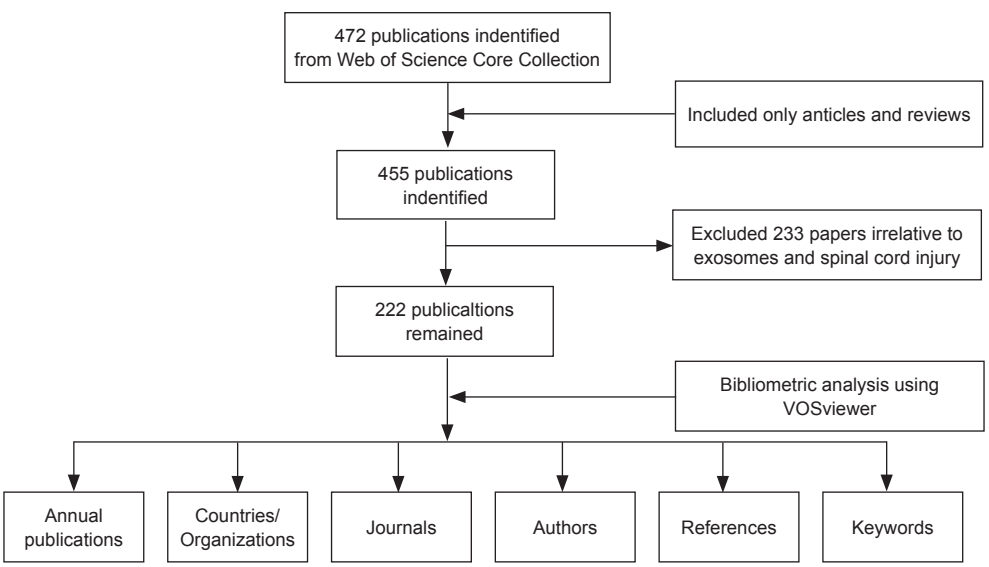

Figure 1. Flowchart of publication screening

Among the 1590 co-cited journals, 52 received more than 60 citations each. Notably, "Journal of Neurotrauma" claimed the top spot in total citations with 517, followed by "Journal of Neuroscience" with 269 citations, "International Journal of Molecular Sciences" with 262 citations, and "Stem Cell Research & Therapy" with 234 citations. Within the top 10 co-cited journals, seven out of 10 (70%) boasted an impact factor exceeding 5, and six out of 10 (60%) were categoriaed within the Journal Citation Reports Q1 zone, indicating their high significance and impact within the scientific community (Table 4).

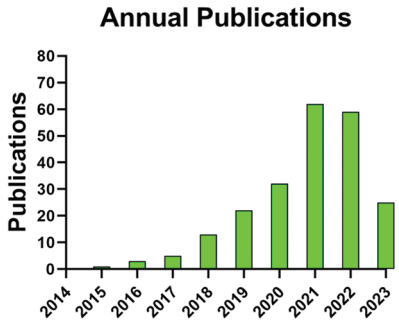

Figure 2. Annual publications on exosomes in spinal cord injury

3.4. Authors and co-cited authors

In this study, 1222 authors contributed to the 222 publications included. Table 5 shows the leading 10 authors, selected on both the number of publication and the number of citations. Each of these authors, with a minimum of four papers authored and

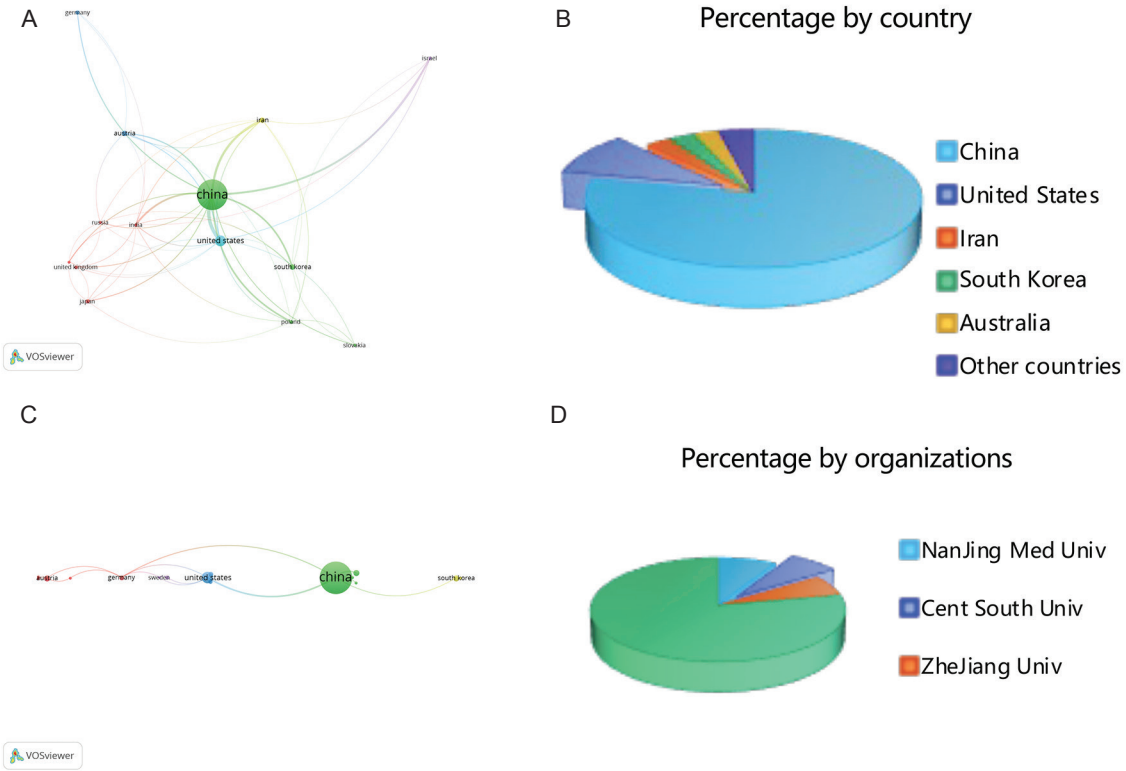

Figure 3. The visualisation of countries (A, B) and organisations (C, D) on research of exosomes of spinal cord injury

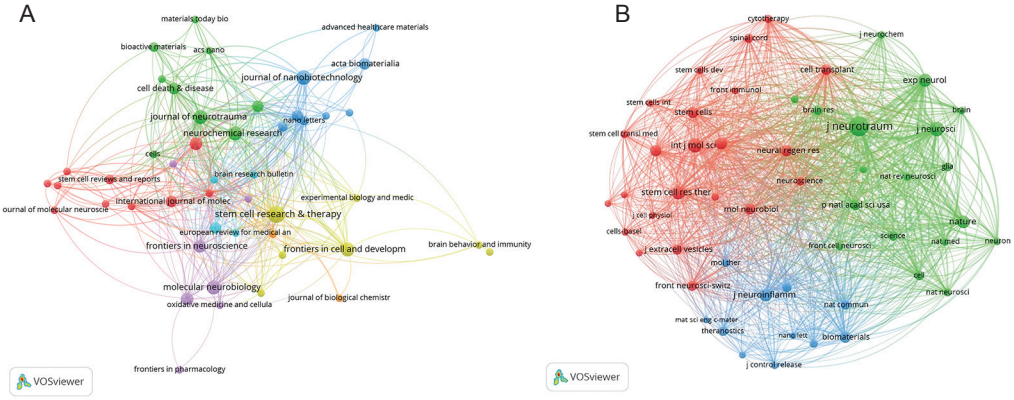

Figure 4. The visualisation of journals (A) and co-cited journals (B) on the research of exosomes of spinal cord injury

Table 1. The top 10 productive countries in the field of exosomes and spinal cord injury

Rank	Country	Documents	Percentage	Total citation	Average citation	Total link strength
1	China	174	78.38	4122	23.69	456
2	USA	22	9.91	762	34.64	191
3	Iran	6	2.70	88	14.67	90
4	South Korea	6	2.70	152	25.33	43
5	Austria	6	2.70	309	51.50	38
6	Germany	4	1.80	56	14.00	17
7	Japan	4	1.80	95	23.75	16
8	Poland	3	1.35	137	45.67	48
9	UK	3	1.35	122	40.67	15
10	India	2	0.90	31	15.50	65

Table 2. The top 10 productive organisations publishing literature related to exosomes and spinal cord injury

Rank	Organisation	Country	Documents	Total citation	Average citation	Total link strength
1	Nanjing Medical University	China	18	842	46.78	255
2	Central South University	China	16	229	14.31	136
3	Zhejiang University	China	14	407	29.07	146
4	Shandong University	China	9	295	32.78	115
5	Fujian Medical University	China	8	281	35.13	150
6	Sun Yat-sen University	China	8	133	16.63	104
7	Xi'an Jiaotong-Liverpool University	China	8	125	15.63	64
8	Nantong University	China	7	76	10.86	120
9	Ministry of Education Key Laboratory for Regenerative Medicine	China	7	166	23.71	62
10	Shanghai Jiao Tong University	China	7	24	3.43	54

Table 3. The top 12 productive journals associated with exosomes and spinal cord injury

Rank	Journal	Count	Percentage	Total citation	IF (2021)	JCR division (2021)
1	*Stem Cell Research & Therapy*	9	4.05	222	8.079	Q1
2	*Journal of Nanobiotechnology*	7	3.15	175	9.429	Q1
3	*Journal of Neurotrauma*	6	2.70	346	4.869	Q2
4	*Frontiers in Cell and Developmental Biology*	6	2.70	81	6.081	Q1
5	*Neurochemical Research*	6	2.70	68	4.414	Q2
6	*Molecular Neurobiology*	6	2.70	91	5.682	Q1
7	*Frontiers in Cellular Neuroscience*	5	2.25	14	6.147	Q1
8	*Frontiers in Neuroscience*	5	2.25	240	5.152	Q2
9	*Neural Regeneration Research*	5	2.25	70	6.058	Q1
10	*Frontiers in Bioengineering and Biotechnology*	4	1.80	13	6.064	Q1
11	*Journal of Neuroinflammation*	4	1.80	232	9.587	Q1
12	*Cell Death & Disease*	4	1.80	253	9.685	Q1

Notes: IF: impact factor; JCR: Journal Citation Reports.

more than 20 citations received (Figure 5A), meets the criteria. Remarkably, the highest number of papers (n = 13) was led by Weihua Cai and Jin Fan, with Wei Liu, Yuluo C Rong, and Jiaxing Wang following closely, each having authored 12 papers. In the author collaboration analysis, 35 authors who had published a minimum of four articles were included, highlighting the collaborative nature and the significant contributions of these authors within the research community (Figure 5B).

Regarding co-citations, 7076 authors were co-cited at least once, with 54 authors receiving co-citations at least 20 times. The most frequently co-cited authors were Liu W with 120 co-citations, Huang JH with 103 co-citations, and both Ahuja CS and Xin HQ with 68 co-citations each. The remaining six leading authors had co-citations ranging from 40 to 61, underscoring their significant influence and contributions to the field, as evidenced by the frequency with which their works are co-cited in other research (Table 6).

3.5. Papers and co-cited references

Out of the 222 papers in the dataset, 148 received more than five citations. Table 7 provides a summary of the most highly cited papers, each having four articles that exceeded 170 citations. The top-ranking papers are authored by Liu W (207 citations), Guo SW (184 citations), Gimona M (173 citations), and Huang JH (171 citations). These authors are accompanied in the top ten list of citations by papers authored by Sun (2018), Liu (2019), Vaccari (2018), Li (2020), Rong (2019), and Lankford. Notably, only one of the 10 articles was published in the Journal of Neurochemistry, and six were from China, highlighting the significant contributions from this region to the field.

Through co-citation analysis, a total of 9027 co-cited references were identified, with co-citation counts ranging from 1 to 65. Within the field of exosomes and SCI, the most frequently cited papers were authored by Huang JH (65 citations), Liu W (59 citations), and Sun GD (53 citations), with citation counts for the remaining top-ranked papers ranging from 30 to 45. Notably, the paper by Liu W, published in the Journal of Neuroinflammation in 2020, stands out as both the most cited and co-cited article, underlining its exceptional significance within this field.

3.6. Keyword co-occurrence

From the co-occurrence analysis, a total of 972 keywords were extracted, offering valuable insights into the prominent areas

Table 4. The most co-cited journals associated with exosomes and spinal cord injury

Rank	Co-cited journal	Total citation	IF (2021)	JCR division (2021)
1	*Journal of Neurotraum*	517	4.869	Q2
2	*Journal of Neuroscience*	269	6.709	Q1
3	*International Journal of Molecular Sciences*	262	6.208	Q1
4	*Stem Cell Research & Therapy*	234	8.079	Q1
5	*Experimental Neurology*	224	5.62	Q2
6	*Journal of Neuroinflammation*	197	9.587	Q1
7	*Nature*	195	69.504	Q1
8	*PLoS One*	190	3.752	Q2
9	*Scientific Reports*	169	4.996	Q2
10	*Biomaterials*	162	15.304	Q1

Note: IF: impact factor; JCR: Journal Citation Reports.

Table 5. The top 10 authors in the field of exosomes and spinal cord injury

Rank	Author	Count	Institution	Location	Total citation	Average	Total link strength
1	Weihua Cai	13	Nanjing Medical University	China	801	61.62	838
2	Jin Fan	13	Nanjing Medical University	China	805	61.92	775
3	Wei Liu	12	Nanjing Medical University	China	800	66.67	792
4	Yuluo Rong	12	Nanjing Medical University	China	800	66.67	792
5	Jiaxing Wang	12	Nanjing Medical University	China	641	53.42	733
6	Guoyong Yin	11	Nanjing Medical University	China	333	30.27	517
7	Yong Cao	10	Central South University	China	359	35.9	298
8	Pengyu Tang	9	Nanjing Medical University	China	439	48.78	592
9	Shiqing Feng	9	Tianjin Medical University	China	74	8.22	202
10	Chengyue Ji	8	Nanjing Medical University	China	425	53.13	527

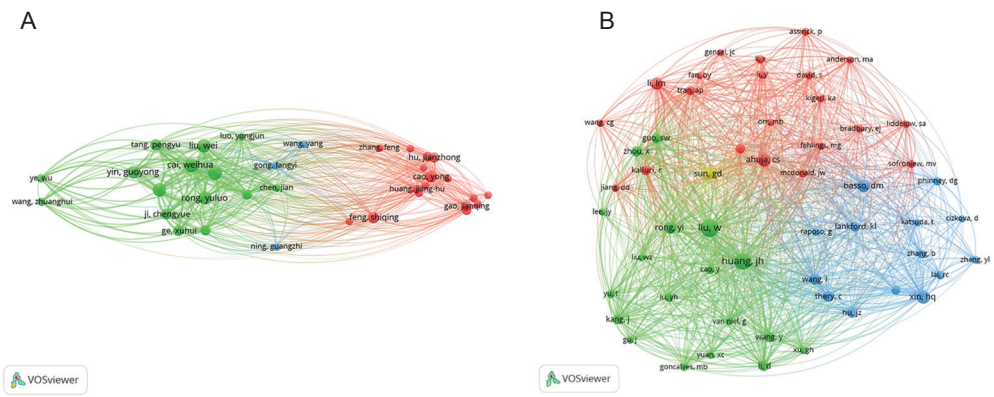

Figure 5. The visualisation of authors (A) and co-cited authors (B) on research of exosomes of spinal cord injury

of focus within the exosomes and SCI field. The keywords that exhibited the highest frequency of co-occurrence included 'spinal cord injury' (161 co-occurrences), immediately followed by 'exosomes' (150 co-occurrences), 'functional recovery' (86 co-occurrences), 'mesenchymal stem cells' (77 co-occurrences), 'extracellular vesicles' (57 co-occurrences), 'inflammation' (50 co-occurrences), 'regeneration' (41 co-occurrences), 'apoptosis' (39 co-occurrences), 'rat model' (37 co-occurrences), and 'expression' (33 co-occurrences). Utilizing keywords that manifested more than 10 instances, a network map was generated, revealing 32 keywords grouped into four colour-coded clusters (Figure 6A–C). These clusters denoted distinct thematic areas, indicating the diverse yet interconnected research directions within the field.

Group 1 (red) centered around topics including angiogenesis, axonal regeneration, bone marrow, functional

Table 6. Top 10 most co-cited authors in the field of exosomes and spinal cord injury

Rank	Co-cited author	Total citation	Institution	Location
1	Liu W	120	Nanjing Medical University	China
2	Huang JH	103	Fujian Medical University	China
3	Ahuja CS	68	University of Toronto	Canada
4	Xin HQ	68	Henry Ford Health System	USA
5	Basso DM	61	Ohio State University	USA
6	Sun GD	58	Jinan University	China
7	Li LM	57	Zhejiang University	China
8	Rong YL	53	Nanjing Medical University	China
9	Thery C	44	PSL Research University, Paris	France
10	Zhou X	40	Shandong First Medical University & Shandong Academy of Medical Sciences	China

Table 7. Top 10 most citied paper in the field of exosomes and spinal cord injury

Rank	Paper	Citation	Journal	Author	Institution	Location
1	Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells repair traumatic spinal cord injury by shifting microglial M1/M2 polarization	207	*Journal of Neuroinflammation*	Liu W	Nanjing Medical University	China
2	Intranasal delivery of mesenchymal stem cell derived exosomes loaded with phosphatase and tensin homolog siRNA repairs complete spinal cord injury	184	*ACS Nano*	Guo SW	Technion Israel Institute of Technology	Israel
3	Manufacturing of human extracellular vesicle-based therapeutics for clinical use	173	*International Journal of Molecular Sciences*	Gimona M	Paracelsus Private Medical University	Austria
4	Systemic administration of exosomes released from mesenchymal stromal cells attenuates apoptosis, inflammation, and promotes angiogenesis after spinal cord injury in rats	171	*Journal of Neurotrauma*	HuangJH	Fujian Medical University	China
5	hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation	161	*Materials Science & Engineering C - Materials for Biological Applications*	Sun GD	Jinan University	China
6	Exosomes derived from bone mesenchymal stem cells repair traumatic spinal cord injury by suppressing the activation of A1 neurotoxic reactive astrocytes	160	*Journal of Neurotrauma*	Liu W	Nanjing Medical University	China
7	Exosome-mediated inflammasome signaling after central nervous system injury	156	*Journal of Neurochemistry*	Vaccari	University of Miami	USA
8	Transplantation of human mesenchymal stem-cell-derived exosomes immobilized in an adhesive hydrogel for effective treatment of spinal cord injury	155	*Nano Letters*	Li LM	Zhejiang University	China
9	Neural stem cell-derived small extracellular vesicles attenuate apoptosis and neuroinflammation after traumatic spinal cord injury by activating autophagy	149	*Cell Death & Disease*	Rong YL	Nanjing Medical University	China
10	Intravenously delivered mesenchymal stem cell-derived exosomes target M2-type macrophages in the injured spinal cord	131	*PLoS One*	Lankford KL	Yale University	USA

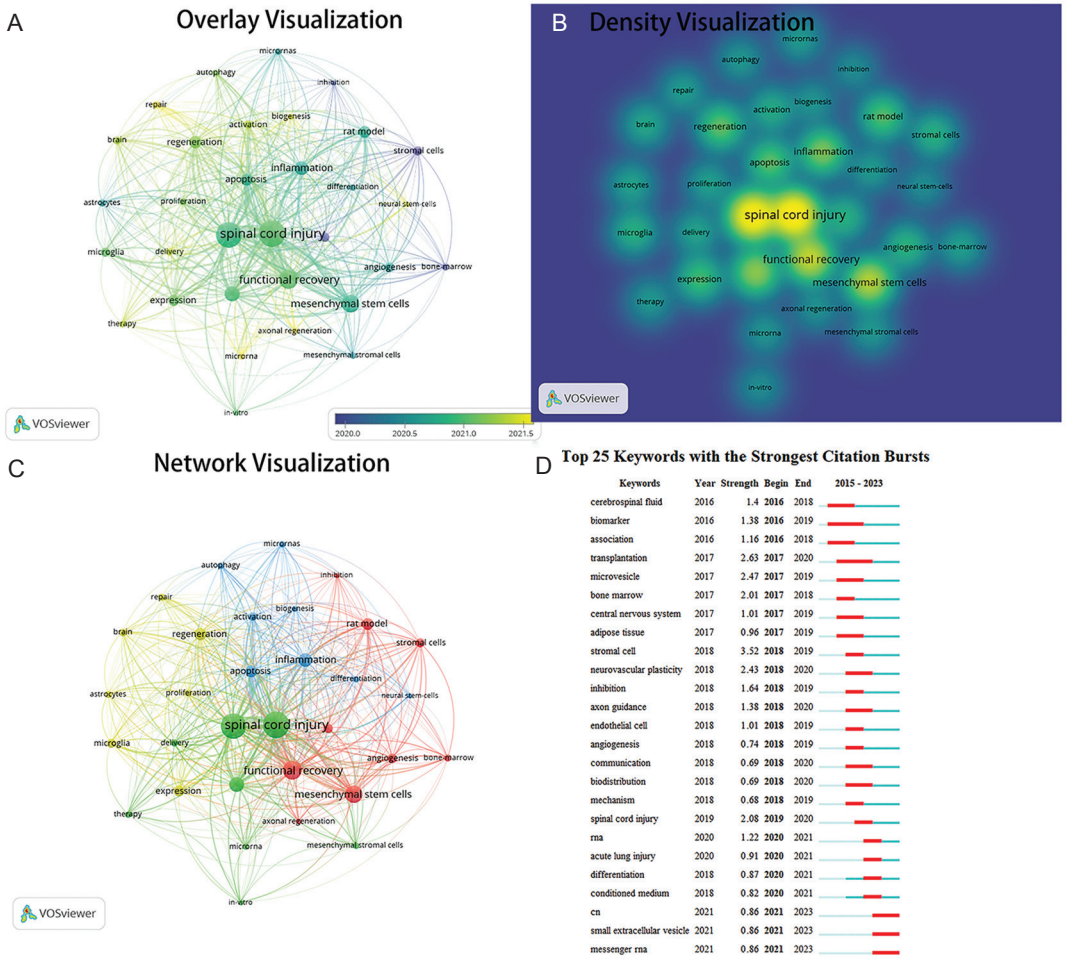

Figure 6. The visualisation of keywords (A–C) and keywords bursts (D) on research of exosomes of spinal cord injury

recovery, inhibition, MSCs, rat models, stromal cells, and transplantation.

Group 2 (green) encompassed keywords such as delivery, exosomes, extracellular vesicles, in-vitro, mesenchymal stromal cells, microRNA, and therapy.

Group 3 (blue) covered activation, apoptosis, autophagy, biogenesis, differentiation, inflammation, microRNAs, and neural stem cells.

Group 4 (yellow) featured terms like astrocytes, brain, expression, microglia, proliferation, regeneration, and repair.

Figure 6D presents the overlay visualisation of the 32 keywords, offering insights into the chronological development of high-frequency keywords.In this visualisation, keywords that gained prominence around the year 2021 are symbolised by yellow nodes. Terms such as 'astrocytes', 'brain', 'expression', 'microglia', 'proliferation', 'regeneration', and 'repair' make up these keywords, collectively indicating current research focal points within the field.

4. Discussion

4.1. General information

In the realm of research concerning exosomes and SCI, the first article was released in 2015, followed by three more in 2016 and five in 2017. Subsequently, from 2018 to 2021, the quantity of publications in this domain consistently ranged between 13 and 62 articles. However, post-2022, there has been a noticeable upsurge in the number of published articles, reaching a notably higher level. In the previous two years, the quantity of published papers consistently surpassed 59, with 25 pertinent articles released in the first half of 2023. This observed trend indicates a growing interest among scientists in comprehending the role of exosomes in the context of SCI.

China and USA stand out as the leading contributors to scholarly articles in this domain, both regarding nations and organisations. China has released a significant 174 articles, representing 78.38% of the overall total, while the United States has contributed 22 articles, representing 9.91% of the publications, thereby considerably exceeding contributions from other nations.

Nonetheless, when considering average citations per article, Austria takes the lead with an impressive average of 51.50 citations per article. It's worth noting that, despite China's high publication volume, its average citation count ranks fourth from the bottom, indicating a need for improved citation impact.

In terms of international collaboration, Austria emerges as the most engaged nation, closely followed by Poland. An

intriguing observation is the affirmative correlation between the intensity of collaboration and the average citation count, suggesting that countries with more extensive international collaborations tend to achieve higher citation impacts for their publications.

Nanjing Medical University in China boasts the greatest quantity of papers released in this domain, with 18 publications, while Central South University in China follows closely with 16 papers. Additionally, it's noteworthy that Nanjing Medical University also excels in terms of average citations, further indicating its significant influence. The average number of citations serves as a valuable indicator of a paper's impact, with higher citation counts reflecting greater influence.

Within the domain of exosomes and SCI research, Stem Cell Research & Therapy emerges as the most productive journal, contributing nine articles, which accounts for 4.05% of the total publications, underscoring its prominence in this domain. Among the periodicals with a notable publication quantity, Cell Death & Disease boasts the highest impact factor at 9.685, closely followed by the Journal of Neuroinflammation at 9.587. Among the top 12 journals based on publication quantity, a significant nine are categorised as top-quartile (Q1) periodicals, indicating their high quality and impact in the scientific community.

When considering co-citations, six out of the top 10 cited journals fall into the Q1 category, while four are classified as Q2. This pattern underscores that influential journals in the realm of exosomes and SCI research tend to have high impact factors, reflecting their significant role and influence within the scientific community.

Among the most productive authors in this domain, those with over 12 publications include Weihua Cai, Jin Fan, Wei Liu, Yuluo Rong, and Jiaxing Wang. Weihua Cai, affiliated with Nanjing Medical University, stands out as the most prolific scholar in this domain, having contributed a total of 13 articles. He is widely recognised as one of the most influential figures in the field. His studies focus on exploring the healing capabilities of exosomes derived from bone marrow MSCs (BMSCs) in the context of SCI. The application of exosomes sourced from BMSCs has shown remarkable effectiveness in alleviating inflammation following traumatic SCI and inhibiting the activation of A1 neurotoxic reactive astrocytes.[4]

In addition to his extensive publication record, Phillip G Popovich is the author of the paper that has received the greatest citation count and co-citations in this domain, titled "Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord".[5] This seminal paper, which was the first to report on the inflammation reaction post-SCI leading to the differentiation of macrophages into M1 and M2 categories, delineated how M1 macrophages induce harm to spinal cord tissue, whereas M2 macrophages facilitate axon regeneration and suppress neuroinflammatory responses. The differentiation condition of macrophages, as elucidated in this study, profoundly affects the prognosis of rats after SCI. This article acts as a foundational piece in SCI research concerning macrophages, forming the basis for subsequent studies on manipulating macrophage polarisation states. In summary, Phillip G Popovich is widely acknowledged as the most impactful researcher in this domain.

4.2. Knowledge base

Co-citation measures the frequency with which two articles are cited together by other research papers. A higher number of co-citations indicates that these papers are considered important foundational articles in the field of exosomes and SCI. In this study, the co-cited top three papers,[4,6,7] the common point of these three articles is that all of them described that utilizing MSC-derived exosomes can significantly reduce the area of SCI and promote the recovery of SCI by attenuating apoptosis and inflammation, promoting angiogenesis, and facilitating axon regeneration, which is expected to be a novel therapeutic strategy for the treatment of SCI. The difference is that Liu W4 used BMSCs exosomes, which, in addition, promote SCI recovery by suppressing the activation of A1 neurotoxic reactive astrocytes. In contrast, Sun et al.[7] used human umbilical cord MSCs and clearly states that human umbilical cord MSC-exosomes improve the prognosis of SCI by down-regulating inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), macrophage inflammatory protein-1alpha (MIP-1alpha), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). In addition, the article also shows that human umbilical cord MSC-exosomes, with an average particle size of 70 nm, can effectively trigger bone marrow-derived macrophage polarisation from the M1 phenotype to the M2 phenotype to promote the inflammation to subside.

The fourth most co-cited article was also authored by Liu W.[8] This study compared the effects on functional behavioural recovery after SCI in mice between two groups: one treated with exosomes derived from MSCs under hypoxic conditions (HExos), and the other treated with exosomes from MSCs under normoxic conditions. The exosomes were characterised using electron microscopy, nanoparticle tracking analysis, and immunoblotting. The results demonstrated that HExos were able to shift microglia polarisation from the M1 to the M2 phenotype both in vivo and in vitro. Furthermore, miR-216a-5p was identified as the most abundant miRNA in HExos. The study suggested that the Toll-like receptor 4 (TLR4)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signalling cascade might be involved in regulating microglia polarisation by hypoxic exosome miR-216a-5p. In conclusion, the findings indicated that HExos could regulate microglia polarisation in mice after SCI, suggesting that hypoxic preconditioning is a promising and effective method to enhance the therapeutic effects of MSC-derived exosomes.

The article[9] has been cited 37 times, ranking 6th. This study describes a novel therapeutic approach wherein exosomes derived from human MSC are immobilised within an adhesive hydrogel. This method effectively releases the implanted exosomes into neural tissues, alleviating inflammatory and oxidative responses while promoting SCI recovery. The co-cited 8th-ranked article, authored by Li et al.,[10] introduces a

new treatment strategy for SCI. It involves encapsulating miR-133b into exosomes secreted by MSCs, activating extracellular signal-regulated kinases 1 and 2 (ERK1/2), signal transducer and activator of transcription 3 (STAT3), and cAMP response element-binding protein (CREB) signalling pathway proteins crucial for neuronal survival and axonal regeneration. Ranked ninth in citations is a systematic review authored by Kalluri et al.,[11] providing comprehensive insights into the biology, function, and medical applications of exosomes. Finally, the 10th-ranked article authored by Lankford et al.[12] introduces the tissue distribution of MSC-derived exosomes in injured spinal cords using 1,1'-dioctadecyl-3,3,3',3'-tetramethylindotricarbocyanine iodide (DiR) fluorescent labeling. This study reveals that these exosomes specifically target M2-type macrophages at the site of SCI.

Among the ten co-cited articles, two were published by Liu and his colleagues[4,8] at Nanjing Medical University, which emphasizes the importance of Liu's research on exosomes in SCI. This also indicates that Nanjing Medical University is a prestigious academic institution focusing on this area, highlighting its leading role and substantial contributions to advancing knowledge and therapeutic approaches in the study of exosomes and SCI.

4.3. The effect of different sources of exosomes in spinal cord injury

In the quest to harness the therapeutic potential of exosomes for SCI management, an intriguing avenue of exploration involves the diverse sources of these tiny vesicles. Exosomes can be derived from different cell types, including BMSCs, adipose-derived stem cell (ADSC), dental pulp stem cells (DPSCs), macrophage/microglia, astrocytes, and other, each with its unique cargo and functional properties. This diversity in origin suggests a wide range of potential therapeutic applications, as the specific content and characteristics of exosomes from different sources may offer unique benefits for SCI treatment and regeneration.[13] Understanding how exosomes from different sources impact SCI is of paramount importance. These distinct exosome populations exhibit varying capabilities in modulating inflammation, promoting neuroprotection, and stimulating tissue regeneration within the injured spinal cord. This article delves into the intriguing realm of exosome diversity, examining how exosomes sourced from various cell types influence the pathophysiology and recovery processes associated with SCI. Through this exploration, we aim to shed light on the complex interactions and potential therapeutic benefits of exosomes in the context of SCI, highlighting their role in influencing outcomes and enhancing recovery (Additional Table 1).

4.3.1. Bone marrow mesenchymal stem cells

For many years, extensive research has focused on BMSCs, particularly within the context of tissue regeneration.[14] However, inherent limitations are associated with BMSCs. Firstly, they demonstrate limited differentiation potential, primarily focusing on mesodermal lineages. This constraint hinders their adaptability in diverse tissue regeneration contexts. Secondly, BMSCs display variability linked to donor age, with variations in both quantity and quality of these cells. Such aging and donor-related disparities may potentially impact their efficacy in therapeutic applications.[15] In recent years, the scientific community has seen rapid advancements in the field of exosomes, revealing their positive impact on SCI repair, especially when sourced from bone marrow MSCs.[16]

Robust potential exists in the ability of exosomes derived from BMSCs to alleviate neuroinflammation.[17] Within a context-dependent microenvironment, M2 macrophages, recognised for their crucial function in tissue regeneration, immune modulation, and immunoregulation, represent a specialised subset of immune cells.[18] BMSCs can induce the generation of M2-like macrophages, also known as EEM (M2-like macrophages derived from BMSCs). M2 macrophages possess anti-inflammatory properties, which aid in neural tissue repair and regeneration. Furthermore, EEMs have the ability to modulate endothelial cell generation and promote axonal growth, thereby facilitating neural functional recovery.[19] The exosomal microRNA-125a derived from BMSCs facilitates the polarisation of M2 macrophages in SCI by suppressing the expression of interferon regulatory factor 5.[20] Exosomal microRNA-124-3p downregulates endoplasmic reticulum to nucleus signaling 1 (Ern1) and promotes M2 macrophage polarisation, thereby ameliorating neural damage in spinal cord ischemia/reperfusion injuries.[21] The efficacy of miR-26a-modified exosomes derived from bone marrow marrow MSCs in promoting axonal regeneration after SCI through the phosphatase and tensin homolog (PTEN)/AKT/mechanistic target of rapamycin (mTOR) pathway has been confirmed by several scholars.[22]

Similar to the blood-brain barrier, the blood-spinal cord barrier (BSCB) oversees the regulation of substance exchange between the bloodstream and spinal cord tissue to uphold a stable and safeguarded microenvironment.[23] The impairment of the BSCB stands as a critical factor obstructing the restoration of motor function subsequent to SCI.[13] Pericytes are essential components of the neurovascular unit, playing a pivotal role in maintaining the structural integrity of the BSCB. Exosomes derived from bone marrow MSCs mitigate neuronal cell death, facilitate neuron survival and regeneration, and enhance motor function recovery. The primary mechanism of action involves restraining pericyte migration, suppressing pericyte pyroptosis, and further enhancing BSCB integrity through the NF-κB p65 signalling pathway within pericytes.[24]

Exosomes derived from bone marrow MSCs can enhance the recovery of SCI by specifically targeting Toll-like receptor TLR4 and inhibiting the NF-κB pathway, thereby facilitating the delivery of microRNA-23b.[25] Moreover, it can also impede neuronal apoptosis and facilitate the recovery of motor function via the Wnt/β-catenin signalling pathway, as well as alleviate disruption of the BSCB following acute SCI through the tissue inhibitor of metalloproteinases 2/matrix metalloproteinase (TIMP2/MMP) pathway.[26] Moreover, exosomes derived from bone marrow MSCs can modulate autophagy by upregulating the protein levels of oligodendrocyte transcription factor 2 (Olig2) and heat shock protein 70 (HSP70) in the injured spinal cord, thereby enhancing autophagy-related proteins and

facilitating spinal cord repair and functional recovery.[15] Some researchers have investigated the modification of exosomesal stem cells to augment the reparative potential for SCI. With regards to complement activation, exosomes derived from bone marrow MSCs can inhibit the synthesis and release of complement mRNA following SCI, thereby exerting a protective role in mitigating spinal cord damage.[27]

In the field of hydrogel technology, researchers have utilized three-dimensional gelatin methacryloyl hydrogels as a carrier for encapsulating exosomes derived from bone marrow mesench stem cells, thereby facilitating the retention and sustained release of exosomes. This approach has demonstrated a significant enhancement in the therapeutic efficacy of SCI treatment.[28]

In conclusion, exosomes sourced from BMSCs have showcased promise as a therapeutic approach for fostering tissue repair and elevating functional recovery after SCI. These promising outcomes are achieved through diverse mechanisms, encompassing signalling pathways, protein expression levels, and the modulation of the BSCB.

4.3.2. Adipose-derived stem cells

The abundance, accessibility, and multipotent capabilities of ADSCs have positioned them as a promising candidate for the treatment of SCI.[29] However, recent research has revealed that the therapeutic effects of ADSCs may not solely stem from their capacity to differentiate into various cell types; instead, considerable attention has been directed towards elucidating the role of extracellular vesicles released by ADSCs, particularly exosomes, in facilitating neurological recovery following SCI.[30]

The therapeutic potential of ADSC-exosomes has demonstrated promising results in various SCI models. Studies indicate that ADSC-exosomes can ameliorate neuronal apoptosis, reduce inflammation, and promote axon regeneration.[29] The study demonstrated that exosomes derived from miR-133b-modified ADSCs effectively facilitated axon regeneration and mitigated apoptosis by modulating specific signalling pathways.[31] Furthermore, another investigation demonstrated that exosomes derived from ADSCs under hypoxic conditions effectively mitigated neuronal apoptosis in rat models of SCI.[29] The findings suggest that the therapeutic potential of ADSC lies in their capacity to modulate crucial cellular pathways and facilitate neural repair.

Moreover, ADSC-exosomes have been studied in the context of autoimmune conditions related to SCI. In an experimental autoimmune encephalomyelitis model, EVs derived from human ADSC have demonstrated the ability to mitigate experimental autoimmune encephalomyelitis by suppressing inflammatory responses and enhancing regulatory T cell function, indicating their potential as a therapeutic approach for multiple sclerosis treatment.[32] The beneficial effects of ADSC-exosomes can be attributed to their role in facilitating intercellular communication and transferring diverse bioactive molecules to target cells. MicroRNA sequencing analysis revealed the presence of miR-511-3p in ADSC-exosomes, which was found to exert a suppressive effect on endoplasmic reticulum stress in rat models of SCI. Moreover exosomes were demonstrated to modulate the TRAF6/S1P axis, thereby offering a novel therapeutic target for SCI.[33]

Furthermore, recent research has emphasized the potential of synergistically integrating ADSC-exosomes with biomaterial scaffolds to effectively facilitate large-area wound healing. ADSC-exosomes have been investigated in vitro to promote cell proliferation and reduce apoptosis, indicating their regenerative potential in wound repair.[34] The utilisation of ADSC-exosomes as readily available tissue engineering products has garnered significant attention, presenting a promising avenue for translating these findings into clinical applications.[35]

The therapeutic potential of exosomes derived from ADSCs in SCI has demonstrated significant promise in preclinical studies. The aforementioned minuscule vesicles possess the capacity to modulate pivotal cellular pathways, facilitate axon regeneration, mitigate inflammation, and alleviate neuronal apoptosis. The ongoing research into the intricate mechanisms underlying their therapeutic effects positions ADSC-exosomes to revolutionize the field of regenerative medicine, offering renewed hope for individuals afflicted with SCI and other neurological disorders. While further research and clinical trials are necessary to validate their efficacy and safety in humans, the potential of ADSC-exosomes as a transformative therapy for SCI remains an intriguing and promising prospect.

4.3.3. Dental pulp stem cells

The role of exosomes derived from DPSCs in SCI has been extensively investigated, with numerous studies focusing on elucidating the underlying mechanisms responsible for their protective effects.[36] Firstly, DPSC-exosomes have demonstrated robust immunomodulatory effects by regulating immune responses and mitigating neuroinflammation. This capability is attributed to the presence of cargo containing immunomodulatory factors, including microRNAs, cytokines, and growth factors.[37], 38 By dampening excessive immune reactions, DPSC-exosomes create a favourable microenvironment for tissue repair and regeneration.

Moreover, DPSC-exosomes have demonstrated their potential to promote angiogenesis. The development of fresh blood vessels is crucial for the repair of tissues. These exosomes carry pro-angiogenic factors that can stimulate endothelial cell proliferation and migration, contributing to improved blood supply in the injured spinal cord region.[38] Additionally, DPSC-exosomes have been found to enhance neurite outgrowth, supporting the reconnection of damaged neural circuits and promoting functional recovery.[39]

A key feature of DPSC-exosomes is their ability to suppress the polarisation of M1 macrophages, a type of immune cell that exacerbates inflammation and tissue damage after SCI.[40] Through the regulation of ROS-MAPK-NF-κBP65 signalling pathway, these exosomes mitigate macrophage-mediated neuroinflammation, preventing further damage to the injured spinal cord.[36]

In conclusion, DPSC-exosomes exhibit immense potential as a therapeutic modality for the treatment of SCI. Their diverse

cargo of bioactive molecules enables them to orchestrate a multifaceted response to the injury, encompassing immunomodulation, angiogenesis, and neural repair. The capacity of these exosomes to regulate the immune response is particularly significant since excessive inflammation often exacerbates SCI damage. By creating an environment conducive to tissue repair and regeneration, DPSC-exosomes offer a novel approach for promoting recovery and functional restoration in SCI patients.

As research progresses in this field, it is anticipated that further elucidation of the specific molecular mechanisms underlying the action of exosomes derived from DPSCs will unlock additional therapeutic potential. Nevertheless, the findings from the reviewed literature have established a robust foundation for future investigations and clinical applications. The exploration of exosomes originating from DPSCs represents a significant advancement in regenerative medicine, offering promising avenues for individuals afflicted with SCI.

4.3.4. Macrophage/microglia

In recent years, studies have unveiled the intricate involvement of macrophage exosomes in the pathophysiology of SCI. Macrophage-exosomes play a pivotal role in orchestrating the inflammatory response and facilitating tissue repair processes following an injury.

The regulation of inflammation is a pivotal function carried out by macrophages, which can undergo polarisation into two distinct subtypes:41 M1 and M2 macrophages represent two distinct subsets. M1 macrophages display pro-inflammatory attributes and play an active role in the initial phases of inflammation. Their production of molecules has the potential to incite tissue harm and draw in additional immune cells to the inflamed area. In contrast, M2 macrophages exhibit anti-inflammatory characteristics and make substantial contributions to tissue repair and regeneration. They achieve this by producing molecules that effectively dampen inflammation while fostering tissue healing.[42] For the maintenance of an optimal immune reaction within the central nervous system, it is crucial to ensure an equilibrium in the proportion of M1 and M2 macrophages.[43] An imbalance in macrophage polarisation has been linked to the development of various neurological disorders. Additionally, macrophage exosomes have surfaced as notable contributors to SCI, with research revealing their therapeutic potential in both inflammation reduction and the facilitation of functional recovery after SCI.[4,7,44] Similarly, microglia-exosomes enriched with miR-151-3p were found to enhance neurological recovery through the inhibition of neuronal apoptosis and promotion of axonal regeneration.[45] These findings suggest that macrophages and microglia are actively involved in the regulation of inflammatory processes following SCI and that exosomes appear to play a crucial role in mediating these interactions.

macrophage-exosomes have also demonstrated the capacity to enhance neuroprotection and promote axonal regeneration following SCI. Microglia-derived exosomal miRNAs, such as miR-151-3p, were identified as key players in inhibiting neuronal apoptosis and promoting axonal regeneration.[45] These exosomes promote miRNA transfer to neurons, and regulate the p53/p21/CDK1 signalling pathway to prevent apoptosis and promote regenerative processes.[45] The potential of macrophage exosomes in enhancing neuroprotection and facilitating axonal regeneration in SCI is underscored by these findings.

In terms of crosstalk and intercellular communication, communication between macrophages and other cell types via exosomes plays a crucial role in the context of SCI. Activated astrocytes were found to release small extracellular vesicles, which induced microglia activation and neuronal apoptosis.[46] In contrast, BMSC exosomes were shown to attenuate astrocyte-mediated inflammation via miR-181c, highlighting bidirectional communication between macrophages and astrocytes in the injured spinal cord.[47] In addition, microglia-derived exosomal miRNAs, such as miR-151-3p, play a key role in neuroprotection of neuronal cells by regulating the p53/p21/cyclin-dependent kinase 1 (CDK1) signalling pathway to attenuate neuronal apoptosis.[45]

In conclusion, macrophage exosomes have emerged as crucial mediators in these processes, potent immunomodulatory effects, promoting neuroprotection, and facilitating axonal regeneration. Through modulation of the inflammatory response, enhancement of phagocytosis communication, In the treatment of SCI, significant therapeutic potential is held by macrophage exosomes. However, further studies elucidate the precise molecular mechanisms and optimize the utilisation of macrophage exosomes as a targeted therapy for SCI.

5. Conclusions

In summary, the bibliometric evaluation performed in this research offers a thorough review of publication production, collaboration trends, influential researchers, and critical research subjectss within the domain of SCI. The results underscore the increasing interest and global engagement in this field, while emphasizing the pivotal role of exosomes in SCI research. These insights have the potential to inform future research initiatives, encourage international collaborations, and advance our comprehension of exosomes' role in SCI pathology and their potential in therapeutic measures.

Limitations of this study: (1) In order to ensure the quality of the literature base, the WOS database is updated relatively slowly, and there may be a small number of articles from 2023 that have not been included in the statistics because they have not yet been included. (2) Due to the language problems, the languages of the literature in this statistics include only English, excluding Chinese, Russian, Italian, Korean, Japanese, etc., and so the works of the scholars from these countries written in their own languages have not been included in the statistics. (3) In the analysis of citation rate, there is a cumulative effect of time in citing rate of an article, and the articles that have been published earlier have more possibilities of obtaining citations.

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Conflicts of interest statement

The authors declare that they have no corporate or financial affiliations that could be interpreted as a potential conflict of interest.

Author contributions

Conceptualization: SZ; *Formal analysis:* LX, HL, FW, CJ and WL; *Writing-original draft:* JS and HX; *Writing-review & editing:* LX, HL, FW, CJ and WL. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Additional file

Additional Table 1: Summary of the therapeutic effects of exosomes from different cell sources on spinal cord injury.

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