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Editorial Board Member of *World Journal of Stem Cells*, Asmat Salim, PhD, Professor, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan. asmat.salim@iccs.edu

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc*.

INDEXING/ABSTRACTING

The *WJSC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, Biological Abstracts, BIOSIS Previews, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJSC* as 3.6; JIF without journal self cites: 3.5; 5-year JIF: 4.2; JIF Rank: 105/205 in cell biology; JIF Quartile: Q3; and 5-year JIF Quartile: Q2. The *WJSC*'s CiteScore for 2023 is 7.8 and Scopus CiteScore rank 2023: Histology is 11/62; Genetics is 78/347; Genetics (clinical) is 19/99; Molecular Biology is 131/410; Cell Biology is 104/285.

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EDITORIAL

Mesenchymal stem cells in wound healing: A bibliometric analysis as a powerful research tool

Vera V Voinova, Daria V Vasina, Anton P Bonartsev

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Abstract

Bibliographic analysis is still very rarely used in experimental basic study papers. The comprehensive bibliometric analysis of scientific literature on research progress and challenges in stem cell therapy for diabetic chronic wounds, which was conducted in the work of Shi *et al* can be a case study and a source of valuable information for writing reviews and experimental papers in this field. Basic experimental studies on a role of mesenchymal stem cells (MSCs) in wound healing that are published in 2023-2024, such as Zhang *et al* in 2023, Hu *et al* in 2023, Wang *et al* in 2023 are certainly also subjects for applying this powerful tool to analyze current research, challenges and perspectives in this field. This is due to the fact that these studies have addressed a great variety of aspects of the application of MSCs for the treatment of chronic wounds, such as using both the cells themselves and their various products: Sponges, hydrogels, exosomes, and genetic constructions. Such a wide variety of directions in the field of study and biomedical application of MSCs requires a deep understanding of the current state of research in this area, which can be provided by bibliometric analysis. Thus, the use of such elements of bibliographic analysis as publication count by year and analysis of top-10 keywords calculated independently or cited from bibliometric analysis studies can be safely recommended for every basic study manuscripts, primarily for the "Introduction" section, and review.

Key Words: Bibliometric analysis; Mesenchymal stem cells; Wound healing; Tissue engineering; Dressing; Hydrogels; Matrix; Exosomes

Core Tip: Bibliographic analysis is still very rarely used in basic studies. Meanwhile, it is a very effective tool to better understand the development of the chosen research area and to analyze the data more broadly, as it is perfectly demonstrated in the work of Shi *et al* in 2024 and in comparisons with basic studies on a role of mesenchymal stem cells in wound healing published. Such elements of bibliographic analysis as publication count by year and analysis of top-10 keywords can be safely recommended for using in every basic study manuscripts.

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INTRODUCTION

As an editor-in-chief, I would like to acknowledge a comprehensive bibliometric analysis of scientific literature on the topic of research progress and challenges in stem cell therapy for diabetic chronic wounds, which was conducted in the work of Shi *et al*[1] in 2024, numerous of basic research papers on this topic of the role of mesenchymal stem cells (MSCs) in chronic wound care published in 2023-2024 years in the *WJSC*. The art of constructing a manuscript of bibliometric analysis allows us to see many important facts and ideas that may remain in the shadows in a manuscript based on the classical format of basic research.

The aim of this work is to try to find elements of bibliometric analysis in conventional basic research papers on this and related topics, and to discern whether the main results of bibliometric analysis on this topic are reflected in the basic research papers. Or, on the contrary, the information presented in ordinary basic research papers contradicts the conclusions of the bibliometric analysis. As a result of this work, we will make recommendations on what role bibliometric analysis should play in experimental study.

BIBLIOMETRIC ANALYSIS

The study of Shi *et al*[1] analyzed the most searched topics within the main research theme in terms of keyword frequency and co-occurrence, as well as papers citations in Scopus, Web of Science Core Collection, VOSviewer, and CiteSpace databases and related software. The results of this study allow identifying the most promising directions in this scientific area: (1) The investigation and application of stem cells for chronic wound healing: “stem cells”, “stromal cells”, “mesenchymal stem cells”, “adipose-derived stem cells”, “endothelial progenitor cells”; (2) The various therapeutic technics for treatment of different diseases associated with chronic wounds: “chronic wounds”, “diabetes mellitus”, “diabetic foot ulcers”, “venous leg ulcers”, “skin”, “double-blind”, “critical limb ischemia”; and (3) The study of mechanisms of wound healing: “diabetic wound healing”, “repair”, “therapy”, “angiogenesis”, ”expression”, “biological therapies”, “differentiation”, “proliferation”.

The authors themselves draw the following conclusions: “The priority topics revolved around dressings, extracellular vesicles, wound healing, and adipose stem cells. The results of these analyses will help researchers understand the current research status and provide hopeful directions for future studies. Future research will also focus on the clinical translation of stem cell therapies for diabetic chronic wounds”.

The authors also conducted a complete bibliometric analysis on parameters such as publication count, country (geographical distribution, country/region contributions), affiliation (author institution, institutional collaboration network), author (authors and cocitation author analysis, contributions of different authors), journal (journals and cocited journal analysis), reference (cocited reference analysis). The tables, graphs, network diagrams, heatmaps compiled by the authors give noticeably clear picture of the current development of the topic on the use of stem cell therapy for diabetic foot treatment in the world biomedical science.

Such analysis is of significant help in planning new research in the chosen scientific field, to correct the direction of research when negative results are obtained, to interpret and discuss the obtained data, and to continue the research in the most promising direction.

BASIC RESEARCH STUDIES IN *WJSC*

Despite the fact that the subject of this manuscript is considerably far from the topic of diabetic foot treatment and is quite specific, considering that the source of biomaterial is deer antlers, nevertheless many key words (from keywords list, abstract or repeatedly occurs in the text) from bibliometric analysis of Shi *et al*[1] we can see in this experimental paper: “wound healing”, “repair”, “therapy”, “mesenchyme/mesenchymal stem cells”, “adipose(-derived) mesenchymal stem cells”, “endothelial (progenitor) cells”, “skin/(cutaneous)”, “(extracellular) matrix”, “(gene) expression”, “(cell) proliferation”. On the other hand, keywords such as “foot ulcer”, “chronic wounds”, “diabetic foot”, “critical limb ischemia”

are missing here, which is not surprising since the investigators used a full-thickness cutaneous wound healing rat model. Also the key word "angiogenesis" is missing in the text, which is rather difficult to explain, since the very process of angiogenesis (by expression levels of CD31 - the surface marker of neovascular endothelial cells) during wound healing is investigated in the paper[2].

In the introduction, the authors also indicate many keywords from the bibliometric analysis and generally describe the current state of research in the field close to the results of the bibliographic analysis, although it is on a more distant topic. The authors draw the conclusion that the use of matrix-based wound covers that injectable hydrogels based on antler reserve mesenchymal matrix have clinical benefits for stimulating regenerative wound healing[2], which partially coincides with the conclusions of the authors of the bibliometric analysis[1]. This paper also includes authors affiliated to Chinese institutions, whereas, according to the bibliographic analysis, China is a leader in this scientific field.

However, in the "Introduction" section, the authors do not make any attempts to conduct a bibliographic analysis of their subject matter.

In this experimental paper, we also see a list of keywords given in the bibliographic analysis[1]: "wound healing", "repair", "mesenchymal stem cells", "endothelial (progenitor) cells", "skin", "angiogenesis", "(cell) proliferation". Although some important keywords (directly from the keyword list) of this research paper[3] are not in the top 10 and top 20 keywords of bibliometric analysis by Shi *et al*[1], they can still be seen in the keywords clustering chart in figure 8A [1], such as "exosomes", "collagen/gelatin" as well as "hydrogel" from the last paper[2]. However, such important keywords of the current research work as "sponge", "safety", "hemostasis", "human umbilical cord mesenchymal stem cells" are totally absent in the bibliometric analysis by Shi *et al*[1].

Meanwhile, the conclusions that the authors draw from the results about high efficacy of MSC-derived exosomes loaded onto gelatin sponges for wound healing[3] largely coincide with the conclusions of the bibliometric analysis[1] that the most promising topics are dressings, stem cells, and extracellular vesicles for wound healing. The authors of this paper are also from China.

In this study, the authors also do not make a bibliographic analysis on their field of knowledge according to any of its parameters (number of papers, keywords, *etc.*).

In this experimental research work[4], we see maximum keyword matching with the bibliometric analysis[1] as this study also investigates the treatment of diabetic ulcers. The list of keywords mentioned in the bibliographic analysis of Shi *et al*[1] in this paper is as follows: "wound healing", "diabetic (foot) ulcers", "diabetes mellitus", "mesenchymal stem cells", "adipose-derived mesenchymal stem cells", "endothelial progenitor cells", "skin", "angiogenesis", "(cell) proliferation", "differentiation", "expression", "mechanism". Moreover, authors are from the Peking Union Medical College from the top 10 of most productive affiliations in this scientific field indicated in the paper of Shi *et al*[1]. The authors' conclusions about the prospective use of modified exosomes partially overlap with the findings of the bibliometric analysis[1].

In this study, the authors also do not make any elements of a bibliographic analysis on their research topic.

Although the topic of experimental basic research of Zhang *et al*[5] in 2024 is not related to diabetic skin ulcers, numerous of keywords are mentioned in this study are from the top 10 and top 20 keywords of bibliometric analysis by Shi *et al*[1]: "(bone marrow) mesenchymal stem cells", "angiogenesis", "differentiation", "repair", "healing", "mechanism", (human umbilical vein) endothelial cells", "proliferation", "therap(eutic)". The authors' conclusions about the prospective use of hydrogel loaded with MSC-derived exosomes partially overlap with the findings of the bibliometric analysis[1].

In this study, the authors do not make a bibliographic analysis on the topic of MSC role in bone regeneration.

RESEARCH PAPERS IN OTHER BPG JOURNALS

The case report of Ha *et al*[6] in 2024 in the *World Journal of Clinical Cases* has only 3 of the same keywords as those noted in the bibliographic analysis of Shi *et al*[1]: "diabetic foot ulcers", "wound healing", and "therapy". The keywords relevant to MSCs are not mentioned in this case report. However, among the important keywords, "regenerative medicine" was not mentioned in the work of Shi *et al*[1].

Some keywords familiar to us from the work of Shi *et al*[1] can be found in another case report of McNeil *et al*[7] in 2023 published in the *World Journal of Diabetes*, such as "diabetic foot ulcer(ation)" and "management". However, the authors of this paper use a specific term "diabetes-related foot disease", derived by them even in the title of the paper, which is not present in the study of Shi *et al*[1]. There are also numerous medical terms in this case report that are not mentioned in the bibliographic analysis of Shi *et al*[1]: "lower extremity amputation", "neuropathy", "arterial disease", "infection".

In the work of Sadat-Ali *et al*[8] in 2023 published in *World Journal of Diabetes* just the main keyword "wound heal(ing)" and the general keyword "mechanism" were indicated, since this case report has nothing to do with either diabetes or MSCs.

Thus, case reports devoted to study of chronic wounds published in other BPG journals are less likely to fall into the keyword pool allocated in the bibliographic analysis of Shi *et al*[1] by their keywords. This is not surprising, as these works are largely outside the scope of bibliographic analysis of Shi *et al*[1].

EXAMPLES

Nevertheless, bibliometric analysis as a special form of scientific research is actively developing in the area of wound healing research. In the last few years, numerous papers of this type have appeared, reflecting the roles of various factors in wound healing: Various drugs (curcumin[9], peptides[10]), different (bio)materials (nanomaterials[11], hydrogels based on alginate[12] and glycol chitosan/silk fibroin/chondroitin-6-sulfate/maleic anhydride-modified polyethylene glycol hydrogel[5]), different cell types (MSCs[1,5], macrophages[13]), diseases (diabetes[1,14], post-COVID-19 fibrosis [15], bone fractures[5]), wound dressing[12], extracellular vesicles[5,16], and biofilms[17]. All these papers are similar to Shi *et al*[1] study in their plan and main content, as well as in the methods of analysis used in the work.

Moreover, with the development of on-line tools for processing bibliographic information in such a database of scientific publications as Scopus, Web of Science, and PubMed, there is a growing trend to bring some simple elements of bibliometric analysis, such as the number of publications by year, into review papers. Such examples of review studies are the following papers in the field of wound care: Pollini and Paladini[18] in 2020, Jaldin-Crespo *et al*[19] in 2022, Nandhakumar *et al*[20] in 2022, Zhang *et al*[21] in 2024.

CONCLUSION

Thus, the bibliographic analysis even on a rather distant topic but in framework of the basic theme devoted to the role of mesenchymal stem cells in wound healing can help in selecting the most promising research direction and in the correct treatment of the current topic. This tool for analyzing scientific information is highly effective. In this regard, we recommend using various elements of bibliographic analysis, which can be found in the study of Shi *et al*[1], at least analyzing the number of papers on a topic by year, top-10 keywords in the chosen research area, and numerous papers by main keywords to write the section "Introduction" of basic experimental study manuscripts and review manuscripts in *WJSC*. Alternatively, one could simply actively refer to such bibliometric analysis studies that are closest in the research topic and cite the most interesting data from them, given into the account that there are already quite numerous studies of this type.

FOOTNOTES

Author contributions: Bonartsev AP designed the research study; Voinova VV, Vasina DV, and Bonartsev AP performed the research; Voinova VV and Bonartsev AP wrote the original draft; Vasina DV and Bonartsev AP reviewed and edited the manuscript; All authors have read and approved the final manuscript.

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SCIENTOMETRICS

Stem cell transplantation in cerebrovascular accidents: A global bibliometric analysis (2000-2023)

Jad El Masri, Ahmad Afyouni, Maya Ghazi, Karim Hamideh, Israe Moubayed, Abdo Jurjus, Hanine Haidar, Ruzanna Petrosyan, Pascale Salameh, Hassan Hosseini

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Abstract

BACKGROUND

Cerebrovascular accident (CVA) is a major global contributor to death and disability. As part of its medical management, researchers have recognized the importance of promising neuroprotective strategies, where stem cell transplantation (SCT) is thought to confer advantages *via* trophic and neuroprotective effects.

AIM

To evaluate the current state of research on SCT in patients with CVA, assess key trends and highlight literature gaps.

METHODS

PubMed was screened for SCT in CVA-related articles in October 2023, for each country during the period between 2000 and 2023. Using the World Bank data, total population and gross domestic product were collected for comparison. VOSviewer_1.6.19 was used to create the VOS figure using the results of the same query. Graphs and tables were obtained using Microsoft Office Excel.

RESULTS

A total of 6923 studies were identified on SCT in CVA, making 0.03% of all published studies worldwide. Approximately, 68% were conducted in high-income countries, with a significant focus on mesenchymal stem cells. The journal "*Stroke*" featured the largest share of these articles, with mesenchymal SCT having the highest rate of inclusion, followed by hematopoietic SCT. Over time, there has been a noticeable shift from *in vitro* studies, which assess stem cell proliferation and neurogenesis, to *in vivo* studies aimed at evaluating efficacy and safety. Additionally, the number of reviews increased along this approach.

CONCLUSION

This bibliometric analysis provides a comprehensive guide for physicians and researchers in the field through an objective overview of research activity, and highlights both current trends and gaps. Having a potential therapeutic role in CVA, more research is needed in the future to focus on different aspects of SCT, aiming to reach a better treatment strategy and improve life quality in patients.

Key Words: Bibliometric analysis; PubMed; Stem cell transplantation; Cerebrovascular accidents; Stroke

Core Tip: This study evaluated the research landscape of stem cell transplantation in patients with cerebrovascular accident, highlighting trends and gaps. Analyzing publications from 2000 to 2023, we found that high-income countries lead stem cell transplantation research, predominantly using mesenchymal stem cells. The journal "*Stroke*" published the most articles. Recent research has shifted from *in vitro* studies to patient-oriented *in vivo* studies focusing on safety and efficacy. This trend indicates a maturing field moving towards clinical application. This study provides a comprehensive overview, guiding future research to optimize clinical outcomes for patients with cerebrovascular accident through stem cell transplantation.

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INTRODUCTION

Cerebrovascular accident (CVA) is a major global contributor to death and disability[1]. Despite advancements in stroke prevention and care, the degree of neurological deficits following a stroke poses a significant medical challenge, underscoring the urgent need for efficient targeted treatments to reduce these profound site effects[2]. Intravenous and intra-arterial thrombolysis can help recanalize occluded arteries in the first hours after the onset of the infarction process which may lessen the severity of brain damage[2]. However, this process also has drawbacks that have prompted the implementation of mechanical thrombectomy, which breaks down the clot physically using stent retriever devices, rather than dissolving them chemically[3]. In parallel, researchers and clinicians have recognized the importance of promising neuroprotective strategies aimed at protecting brain cells from damage. Nevertheless, the discovery of effective cytoprotective agents has proven challenging[4,5].

The above results spurred efforts to find alternative treatments, which have recently focused on restoring brain function through cell transplantation. Adult stem cells serve as a promising source of cells for regenerative medicine, particularly in the context of neurological diseases such as stroke. Data from animal models suggest that these cells have the capacity to replace damaged or dysfunctional cells and contribute to tissue repair and functional recovery[6-9]. The spectrum of cells currently used in these studies includes bone marrow, mesenchymal, umbilical, fetal, and embryonic cells[10].

Beyond the replacement of infarcted tissues, transplanted cells are thought to confer advantages *via* trophic and neuroprotective effects. The release of trophic factors by neurons and nonneuronal cells in stumps of the denervated distal nerves enriches the local neural environment by sustaining synaptic connections and enabling host axonal regeneration[11]. Moreover, grafts have also been suggested to stimulate surviving cells to build new neural circuits by supplementing endogenous recovery mechanisms, which include neurogenesis and angiogenesis[12]. Although the immense success seen in preclinical models is uplifting, clinical trials have yet to yield the same results. Many issues still need to be addressed, and much research is still required before this treatment can be widely available[13].

Despite these challenges, stem cell transplantation (SCT) holds great promise for treating CVA. With continued research and innovative development in this dynamic domain, this treatment could in the near future revolutionize medicine and improve the lives of millions of people. Therefore, the purpose of this study is to evaluate the current state of research on SCT in patients with CVA and to assess trends as well as highlight any gaps in the literature.

MATERIALS AND METHODS

Database and search strategy

Searches for SCT in CVA-related articles were conducted on October 25, 2023, for each country worldwide, with a time limit between 2000 and 2023. We used PubMed, a free search engine that primarily accesses the MEDLINE database of references and abstracts on life sciences and biomedical topics. PubMed keywords search offers optimal update frequency and includes online early articles rendering it the optimal tool in biomedical electronic research[14]. Similar studies have been conducted in different specialty fields and for different regions[15-17].

Interpretation and comparison

The PubMed database was searched using the following keywords and free-text terms combined with boolean operators (AND, OR): ("Stem cells"[Medical Subject Headings (MeSH) Terms] OR "Stem Cell Transplantation"[MeSH Terms] OR "stem cells"[All Fields] OR "Stem cells transplantation"[All Fields] OR "stem cell therapy"[All Fields] OR "stem cell transfer"[All Fields]) AND ("Stroke"[MeSH Terms] OR "Cerebrovascular Trauma"[MeSH Terms] OR "Brain Ischemia"[MeSH Terms] OR "Intracranial Hemorrhages"[MeSH Terms] OR "brain hemorrhage, traumatic"[MeSH Terms] OR "Cerebrovascular Disorders"[MeSH Terms] OR "cerebrovascular accident"[All Fields] OR "Stroke"[All Fields] OR "traumatic brain hemorrhage"[All Fields] OR "ischemic brain injury"[All Fields]) AND 2000/01/01: 2023/12/31[Date - Publication]. The affiliation of authors was used to track the country of publication and create the map using mapchart.net[18]. Based on the World Bank classification, studies from each country were classified as high-income, upper-middle-income, low-middle-income, and low-income countries[19].

The gross domestic product (GDP) and the population size were acquired from the World Bank data website[20]. Taiwan's GDP was obtained from tradingeconomics.com and its population from macrotrends.net. We calculated the average GDP and population for the top 20 countries between 2000 and 2023 and obtained the publications per average GDP (in 100 billion USD) and the publications per million population.

The contribution of the top five active countries mentioning one type of SCT was obtained using the search strings mentioned above AND the "MeSH term" for different types of transplantation. The contribution of the top 20 clinical neurology journals according to Scimagojr.com was determined using the aforementioned search strings AND the term of each journal[21]. VOSviewer_1.6.19 was used to create the VOS figure using the results of the same query. Graphs and tables were obtained using Microsoft Office Excel.

RESULTS

Figure 1 shows the distribution of research articles published on SCT in CVA worldwide between 2000 and 2023. The United States and China had the highest productivities with several articles ranging between 1000 and 2000. By contrast, many countries had minimal productivity. Most African and some Asian countries, along with Greenland, had zero articles. According to Figure 2, approximately two-thirds (69%) of the articles related to SCT in CVA were contributed by high-income countries, while almost none (0.04%) by low-income countries. Besides, around one-third of the articles were contributed by upper-middle and lower-middle income countries (26.67% and 4.5%, respectively).

A total of 6923 studies were identified on SCT in CVA, making 0.03% of all published studies worldwide. The United States ranked first worldwide with respect to the number of articles on SCT in CVA, with 1681 articles (Table 1) accounting for 24.28% of the total research on SCT in CVA. China ranked second with 1476 articles accounting to 21.32%, followed by Japan with 543 articles accounting to 7.84% of total articles. Germany and Canada ranked fourth and fifth, respectively. On the other hand, research on SCT in CVA constituted less than 0.1% of the total articles in each of the top 20 countries, with South Korea having the highest percentage of 0.08%, Georgia second with 0.062%, and Taiwan third

Table 1 Top 20 performing countries with research articles on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023

Rank	Country	Number of articles on SCT in CVA	Percentage among total articles on SCT in CVA	Total number of articles	Percentage of articles on SCT in CVA among total articles	Number of articles per GDP (100 billion USD)	Number of articles per million population
1	United States	1681	24.28%	4522491	0.037%	10.30	6.53
2	China	1476	21.32%	2710209	0.054%	18.72	1.34
3	Japan	543	7.84%	1146807	0.047%	10.90	4.59
4	Germany	387	5.59%	1140393	0.034%	11.62	4.85
5	Canada	239	3.45%	804341	0.030%	16.20	8.52
6	Italy	163	2.35%	875969	0.019%	8.48	2.88
7	Taiwan	154	2.22%	261548	0.059%	32.63	6.66
8	Spain	151	2.18%	588135	0.026%	12.17	3.81
9	France	150	2.17%	780901	0.019%	6.13	2.57
10	Sweden	142	2.05%	325489	0.044%	29.79	16.27
11	Iran	136	1.96%	248208	0.055%	38.90	2.51
12	Australia	119	1.72%	682640	0.017%	10.97	6.80
13	Netherlands	113	1.63%	512315	0.022%	14.33	7.56
14	India	99	1.43%	654887	0.015%	5.79	0.11
15	Georgia	86	1.24%	137776	0.062%	692.04	20.68
16	Poland	83	1.20%	234641	0.035%	18.60	2.29
17	South Korea	83	1.20%	104065	0.080%	6.81	1.99
18	Brazil	82	1.18%	424567	0.019%	5.18	0.55
19	United Kingdom	79	1.14%	343056	0.023%	3.03	1.34
20	Belgium	64	0.92%	247924	0.026%	14.07	6.27

CVA: Cerebrovascular accident; GDP: Gross domestic product; SCT: Stem cell transplantation; USD: United States dollar.

with 0.059%[1]. This percentage was lowest in India (0.015%), and slightly higher in Australia, Brazil, and Italy (0.017%, 0.019%, and 0.019%, respectively). Georgia by far had the highest number of articles per GDP (100 billion USD) at 692.04. Second and third were Iran (38.90) and Taiwan (32.63). This number was the lowest in the United Kingdom (3.03). Regarding the number of articles per million population, Georgia again ranked first with 20.68 articles, followed by Sweden with 16.27 and India ranked last (20th) with only 0.11 articles.

Figure 3 shows the evolution of the number of articles between 2000 and 2023 among the top five countries with the highest contributions to SCT in CVA research. The United States exhibited a steady increase over the years, peaking at about 150 articles in 2019, followed by a steep decline to approximately 50 articles in 2023. China experienced a sharper increase, peaking at almost 175 articles in 2022, with a subsequent decline to slightly less than 150 in 2023. Japan, Germany, and Canada showed a modest increase over the years, each reaching 50 articles per year. These three countries also peaked in recent years and have seen a significant decline over the last 2 years. Overall, it appears that productivity, as measured by the number of articles, has declined in the last 3-4 years across all these countries.

Table 2 shows the number of retrieved articles published in each of the top 20 clinical neurology journals. "*Stroke*" had the highest number of articles, totaling 165. In comparison, "*Annals of Neurology*" and "*Brain*" were ranked second and third, with a maximum of 27 and 22 articles, respectively. Notably, 6 of the top 20 journals had no articles published on SCT in CVA. On the other hand, Figures 4 and 5 depict the frequency of inclusion of each type of SCT in CVA research. Mesenchymal SCT was the most frequently mentioned term among these articles (63.0%). It accounted for 140 articles by the United States, 270 by China, 80 by Japan, 30 by Germany, and 20 by Canada. Hematopoietic SCT was the second most frequently used term (24.1%). The United States contributed with about 90 articles, Japan with 30 and China, Germany, and Canada with 20 articles each. Cord blood SCT was mentioned in 10.4% of articles, mainly by the United States and China, whereas peripheral blood SCT was included in 2.5% of articles, mostly contributed by Japan.

Network of co-occurrence of clusters

Network visualization of MeSH keywords co-occurrence revealed four main clusters. The first one, in red color, focused

Table 2 Distribution of articles published on stem cell transplantation in patients with cerebrovascular accident by journal between 2000 and 2023

Ranking	Journal	Number of articles
1	*The Lancet Neurology*	9
2	*JAMA Neurology*	1
3	*Nature Reviews Neurology*	3
4	*Molecular Neurodegeneration*	2
5	*Acta Neuropathologica*	4
6	*Neuro-Oncology*	3
7	*Brain*	22
8	*Annals of Neurology*	27
9	*Alzheimer's and Dementia*	0
10	*Journal of Neurology, Neurosurgery and Psychiatry*	4
11	*Autism in Adulthood*	0
12	*Sleep Medicine Reviews*	0
13	*Stroke*	165
14	*European Stroke Journal*	0
15	*Annual Review of Vision Science*	0
16	*Alzheimer's Research and Therapy*	1
17	*Movement Disorders*	1
18	*Translational Neurodegeneration*	0
19	*Neurology*	20

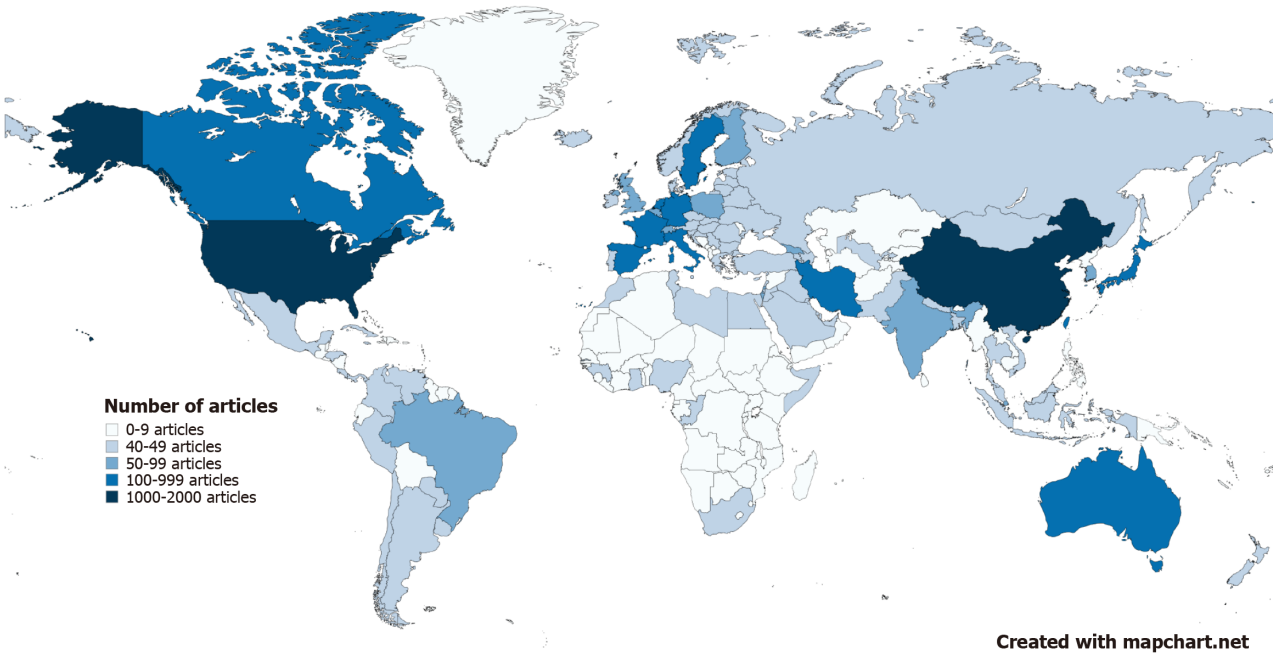

Figure 1 Global research productivity on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023.

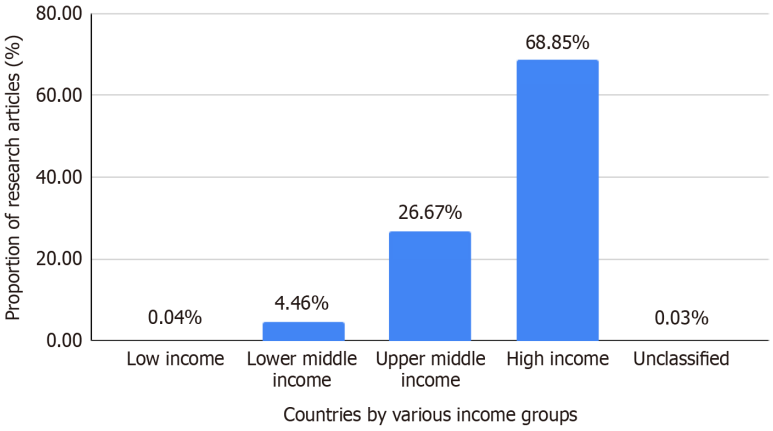

Figure 2 Proportion of research articles on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023 by various income group countries.

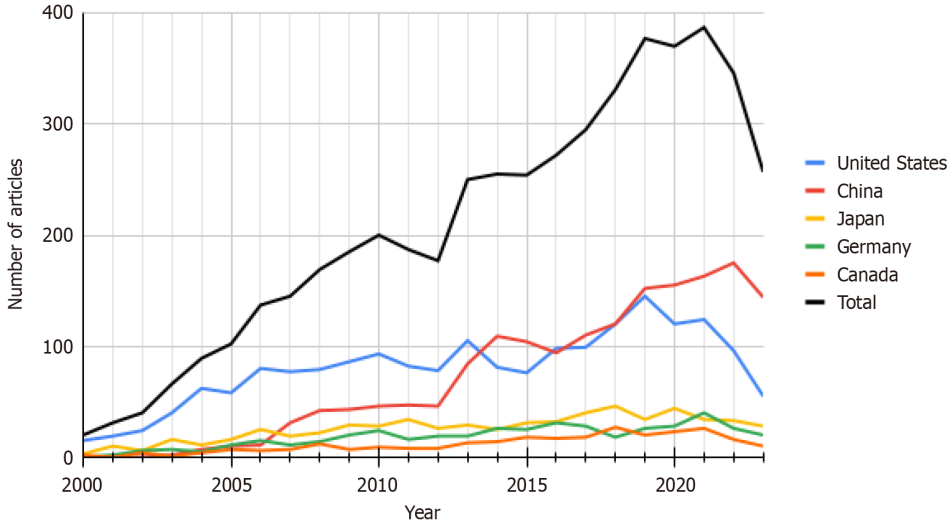

Figure 3 Publication trend among the top five countries on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023.

on neurogenesis-related keywords and comprised the terms: proliferation, neural progenitor cell, subventricular zone, and apoptosis. The second cluster, shown in blue, focused on the patient and contained the terms: Study, trial, efficacy, safety, acute myocardial infarction, and heart failure. The third cluster, in green, addressed the disease and included the following keywords: Hematopoietic stem cell transplant, review, research, progress, risk, and neurological disease. The last cluster, colored in yellow, targeted SCT and included the terms: Meta-analysis, systemic review, mesenchymal stem cell therapy, and stroke patient (Figure 6). The co-occurrence of MeSH keywords using the overlay visualization option on VOSviewer showed that articles around the world on SCT and CVA shifted around 2012 from focusing on stem cells and SCT, moving to proliferation and neurogenesis in 2014, with more patient-oriented research. This was followed by studies on various diseases and stem cell therapy in 2016, with more focus on efficacy and safety. In 2018, different types of stem cell therapy (mesenchymal for example) were introduced, along with meta-analyses and reviews (Figure 7).

DISCUSSION

The potential of stem cells to repair damaged tissue and improve neurological function has provided an impetus for researchers to investigate this emerging field. On this basis, we examined the state of the literature on SCT for patients with CVA over the past two decades. The increasing popularity of this field was particularly noted in developed countries such as the United States, China, and Japan, consistent with the leading countries in life sciences research worldwide[22]. The number of papers produced from the United States and China is nearly three times higher compared to Japan. Approximately 68% of the research was done in high-income countries, with mesenchymal stem cells being the most extensively studied. Research focus shifted from *in vitro* studies, assessing stem cell proliferation and neurogenesis, to *in vivo* studies, targeting efficacy and safety, and the number of reviews increased.

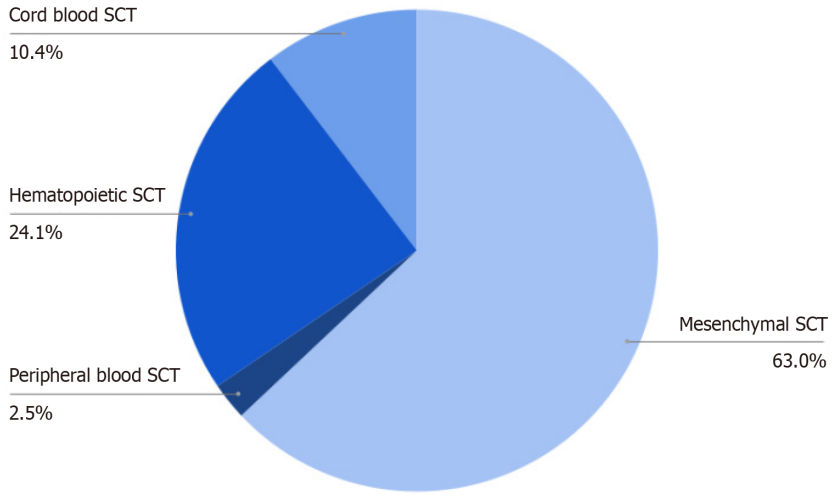

Figure 4 Percentage of articles mentioning each type of stem cell transplantation in patients with cerebrovascular accident. SCT: Stem cell transplantation.

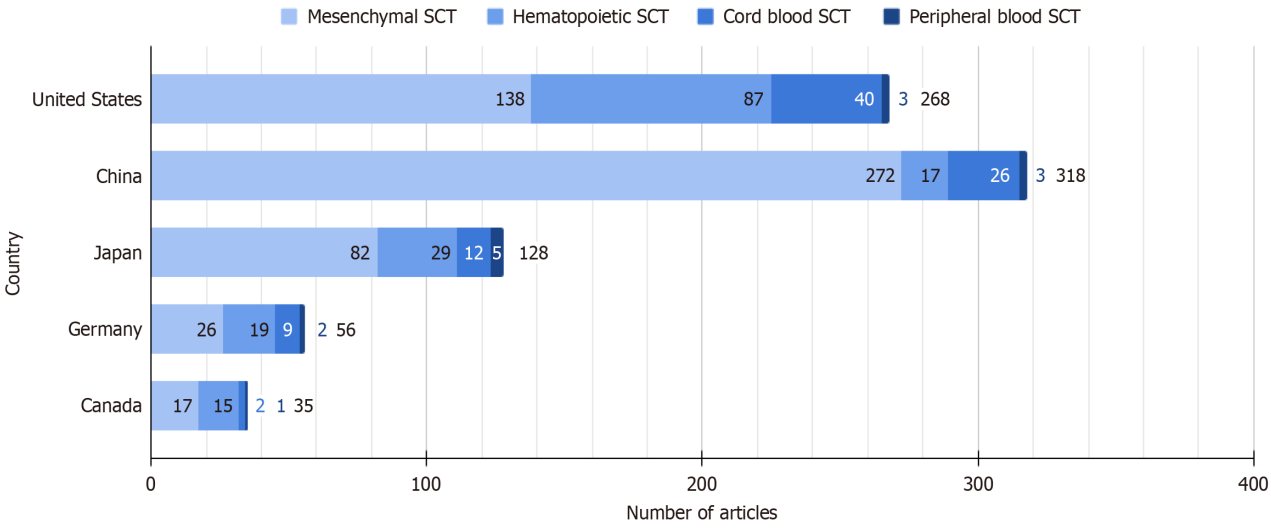

Figure 5 Contribution of the top five active countries for each type of stem cell transplantation in patients with cerebrovascular accident. SCT: Stem cell transplantation.

Despite the positive correlation between stroke and low sociodemographic status, as well as the increase in cases in low-income countries compared to a decrease in high-income countries, the majority of research was done in high and middle high-income countries[23]. Stem cell therapy is an expensive protocol that requires extensive research to reach the targeted therapeutic stage, thus requiring a large amount of funding[24-26]. This might explain our findings, as higher-income countries typically have larger budgets, better infrastructure with more advanced technology, and can afford to invest more in research on SCT, as well as to support expensive therapy protocols once approved[27,28].

When following the trends in research on stem cell therapies in CVA, a decline can be noticed around 2020. This decline could be linked with the coronavirus disease 2019 pandemic, which had a major impact on research productivity worldwide[29]. The pandemic also led to an overall shift or decrease in research productivity, as many researchers have been forced to work from home or had their research projects delayed or canceled[30]. Despite the increase in stroke cases due to the potential of the virus to cause blood clots in the brain's vasculature in around 2% of coronavirus disease 2019-infected patients, research efforts shifted towards more prevalent complications, leading to this decrease in research productivity concerning SCT[31,32]. Moreover, *Stroke* was found to be the leading journal in the field of stem cell therapy for stroke. The countries with the highest number of publications in this journal are United States, Japan, and Germany, which is consistent with our findings[33].

Main keywords that have received extensive attention in this field during the past 5 years included "mesenchymal stem cell therapy," "clinical target," and "therapeutic target." When compared to an earlier era, "hypoxia-ischemia" and "adult rat" were the main keywords. This shift reflects the ongoing transformation from preclinical findings to clinical trials. Stem cell research has shifted to concentrating on "human pluripotent stem cells," "mesenchymal stem cell therapy," and "neural stem cell (NSC)." Since stroke recovery relies heavily on the regeneration of nerves and blood vessels, the formation of the neurosphere from NSCs opened up new possibilities for the regenerative treatment in CVA

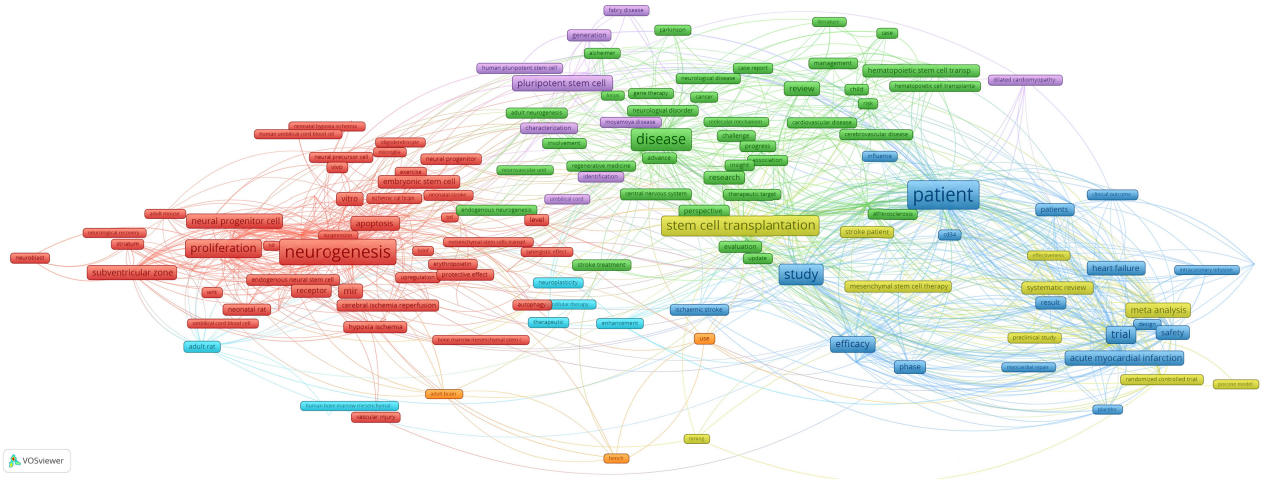

Figure 6 VOSview of the main occurrences of stem cell transplantation in patients with cerebrovascular accident in articles between 2000 and 2023.

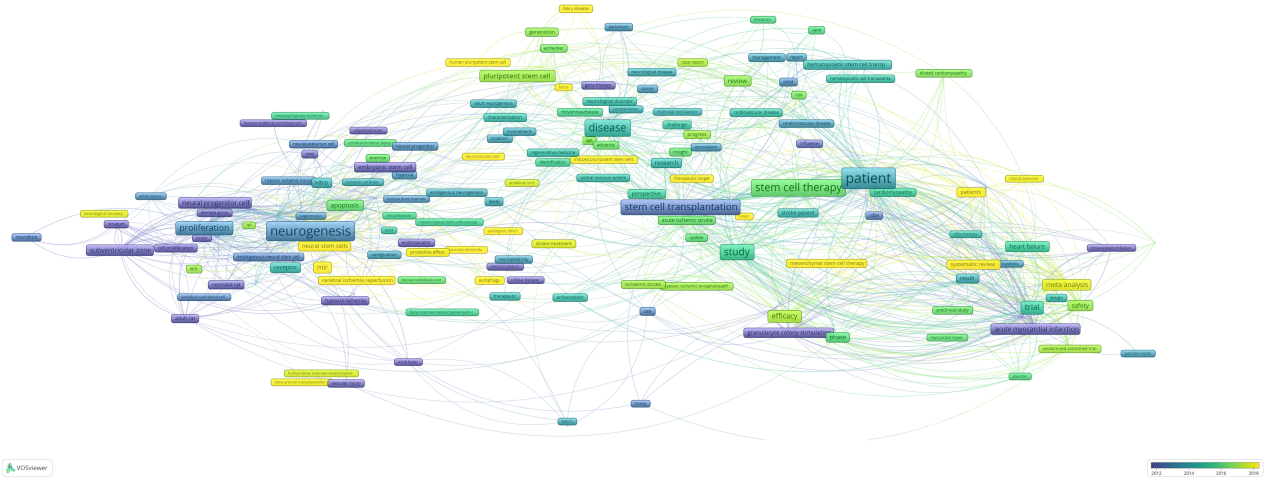

Figure 7 VOSview of the main occurrences of stem cell transplantation in patients with cerebrovascular accident concerning articles between 2000 and 2023.

patients[34].

Regarding mechanistic and molecular factors in stem cell therapy, the results presented highlight a wide gap in this field. For example, cell microenvironment, immunity, genetic and epigenetic stability, scaffolding methods, and regulatory and signaling pathways were minimally targeted, as shown in Figures 6 and 7[35-37]. Even in regard to the few molecular and mechanistic factors that were mentioned, such as Wnt, MIR, brain-derived neurotrophic factor, tumor necrosis factor and cluster of differentiation 34, their discussion was to a lesser extent compared to other clinical and epidemiological factors that were highly tackled. Playing a major role in the effectiveness of stem cell therapy, these factors need to be more studied and targeted in future studies, aiming to reach better outcomes in CVA cases.

In recent years, research on "case reports" has steadily gained popularity, indicating that researchers have been delving further into implementing stem cell therapy. For instance, a phase 1 clinical trial observed neurological improvement after the delivery of single intracerebral doses of the NSC line CTX0E03, with no adverse events. However, only 11 men were recruited in this study[38]. This suggests that further investigation with a larger patient population is needed.

To the best of our knowledge, this study is the first bibliometric analysis to assess research trends regarding stem cell therapy in stroke. However, several limitations should be noted. For instance, only a single database (PubMed) was searched. Despite being one of the largest databases, PubMed does not index all journals, which may have led to the omission of some articles. Furthermore, only papers written in English were included, excluding the very few published in other languages[5]. Finally, while this bibliometric analysis describes research trends on this topic, the content of each paper was not critically analyzed.

CONCLUSION

This article assessed global research trends and activity regarding literature on SCT in CVA. It provides a comprehensive guide for physicians and researchers in the field through an objective overview of research activity. This bibliometric analysis highlights both current trends and gaps, offering a roadmap for guiding future research efforts to ultimately achieve the most beneficial clinical outcomes. Having a potential therapeutic role in CVA, more research is needed in the future to focus on different aspects of SCT, aiming to reach a better treatment strategy and improve life quality in patients.

FOOTNOTES

Author contributions: Masri JE and Ghazi M conceptualized the study; Masri JE, Afyouni A, Hamideh K, and Hosseini H extracted and organized the data; Masri JE, Afyouni A, Hamideh K, and Jurjus A performed the data analyses; Masri JE, Afyouni A, Hamideh K, and Petrosyan R designed the methodology; Salameh P and Hosseini H supervised the study; Masri JE, Afyouni A, Ghazi M, Moubayed I, and Jurjus A wrote the original draft of the manuscript; Jurjus A, Haidar H, and Hosseini H reviewed and edited the manuscript.

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LETTER TO THE EDITOR

Mechanism of mesenchymal stem cells in liver regeneration: Insights and future directions

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Abstract

Mesenchymal stem cells (MSCs) are a prevalent source for stem cell therapy and play a crucial role in modulating both innate and adaptive immune responses. Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of triglycerides in liver cells and involves immune system activation, leading to histological changes, tissue damage, and clinical symptoms. A recent publication by Jiang *et al*, highlighted the potential of MSCs to mitigate in NAFLD progression by targeting various molecular pathways, including glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. In this editorial, we comment on their research and discuss the efficacy of MSC therapy in treating NAFLD.

Key Words: Mesenchymal stem cells; Liver regeneration; Non-alcoholic fatty liver disease; Immune cells; Therapeutic strategy

Core Tip: This editorial discusses a recent article published in the *World Journal of Stem Cells*, which presents mesenchymal stem cells as a promising therapeutic approach for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. The study emphasizes targeting key molecular pathways such as glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. We provide insights into their findings and explore relevant topics in this field.

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TO THE EDITOR

The liver, a central metabolic organ and a key component of the human immune system, is highly susceptible to pathogen-induced acute or chronic liver injury[1]. It harbors a dense population of myeloid and lymphoid immune cells, and disruption of liver immune homeostasis is frequently associated with various liver diseases[2]. Following liver injury, different subsets of innate immune cells such as - macrophages, natural killer (NK) cells, NKT cells, γδ T cells, dendritic cells, innate lymphoid cells, neutrophils, and eosinophils - and adaptive immune cells, including T lymphocytes, regulatory T cells, B lymphocytes, and T helper cells, become activated[3]. End-stage liver disease is marked by extensive damage to the liver parenchymal cells, resulting in liver dysfunction and irreversible liver failure. Conventional liver therapies are often fall short in treating these conditions, making liver transplantation the only effective treatment option for end-stage liver disease[4]. However, the clinical utility of liver transplantation is limited by high costs, organ shortages, surgical risks, potential immune rejection post-transplantation, and relatively low success rates. Moreover, even in cases of successful transplant cases, patients must take immunosuppressive drugs for life, which imposes significant economic and emotional burdens.

Mesenchymal stem cells (MSCs) are pluripotent stem cells capable of homing to target tissues and releasing various factors that can modify or enhance damaged tissue function[5]. MSCs can be isolated from multiple sources, including bone marrow, adipose tissue, peripheral blood, synovial membrane tissue, and cartilage[6]. These cells can differentiate into mesodermal lineages, such as adipocytes, osteocytes, and chondrocytes[7]. MSCs exhibit self-renewal, pluripotent differentiation, and low immunogenicity, making them pivotal for tissue repair. MSCs transplantation, as well as the use of MSC derivatives such as exosomes or conditioned medium, has proven effective in resolving inflammation, oxidative stress, fibrosis, and the accumulation of fatty acids and triglycerides in various non-alcoholic fatty liver disease (NAFLD) mouse models[8-11]. Recent clinical studies have demonstrated that MSC therapy alleviates liver damage, improves liver function, and promotes liver tissue regeneration[12,13]. Furthermore, liver stem cell transplantation, which can generate mature hepatocytes with self-proliferation capabilities, is currently considered a potential adjuvant treatment for end-stage liver diseases[14]. Numerous studies have confirmed the effectiveness of stem cells, particularly MSCs and induced pluripotent stem cells, in treating liver failure[15]. For auto-immune hepatitis, MSCs are especially effective due to their immune regulatory properties and significant repair capabilities[16]. One study has shown that MSC-mediated modification of the fiber domain allows the virus to replicate effectively in a hepatocellular carcinoma vector, while the hypoxic response of viruses weakens cancer cell growth, ultimately enhancing the antitumor efficacy against hepatocellular carcinoma[17].

In a recent publication titled "Current perspectives on mesenchymal stem cells as a potential therapeutic strategy for non-alcoholic fatty liver disease", the authors elucidated how MSCs can attenuate the progression of NAFLD[18]. The review offers a comprehensive overview of the therapeutic potential of MSCs in NAFLD, addressing various aspects such as the mechanisms of action, therapeutic potential, and the roles of MSCs in treating different facets of NAFLD by regulating molecular pathways related to glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. Despite extensive documentation of MSC effects on liver regeneration, our understanding of the mechanisms through which MSCs promote hepatocyte regeneration remains limited.

Mechanism of MSCs in liver regeneration

It has been demonstrated that culturing MSCs with specific growth factors enables their differentiation into hepatocyte-like cells (HLCs) with liver-specific morphology and functions. These HLCs exhibit several characteristics, including the ability to uptake low-density lipoproteins and indocyanine green, secrete albumin and urea, store glycogen, and display cytochrome P450 activity[19]. Moreover, HLCs target the injury site by releasing exosomes, which help restore liver homeostasis and enhance hepatocyte function[20]. Studies have shown that MSCs migrate to the site of liver injury sites and secrete growth factors and cytokines with paracrine effects, thereby promoting liver regeneration. MSCs release various anti-apoptotic growth factors, such as stromal cell-derived factor-1, basic fibroblast growth factor, vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-I, to prevent hepatic stellate cell activation and subsequent liver fibrosis[21,22]. MSCs also express numerous chemokine receptors that facilitate their localization to inflammatory sites through interaction with inflammatory chemokines and cytokines. Additionally, the presence of CD44 on the surface of MSCs enables their binding to E-selectin on endothelial cells, facilitating their migration to injury sites to promote regeneration of damaged liver cells[23]. Furthermore, MSCs enhance angiogenesis through paracrine effects, which improve venous endothelial cell proliferation, migration, and angiogenesis, while also enhancing the oxygen and nutrient supply and growth factor release in damaged tissues to support regeneration[24].

MSCs also regulate immune responses by inhibiting the activation of innate immune cells, such as macrophages, NK cells, NKT cells, dendritic cells, and monocytes, while modulating the activity of adaptive immune cells. They suppress the activation of T cell, B cell, and NK cells, reduce the expression of NK group 2, member D, decrease alanine aminotransferase and pro-inflammatory cytokine levels, and alleviate inflammatory cell infiltration in the liver[25]. Additionally, MSCs inhibit T cell and B cell proliferation, induce immunotolerance, promote regulatory T cell deve-

lopment, and suppress antibody production, secretion, and activated B cell proliferation in the adaptive immune system [26].

CONCLUSION

The study conducted by Jiang *et al*[18] is significant not only for highlighting the potential of MSCs as a therapeutic approach for NAFLD, a prevalent and complex liver condition with limited treatment options. It provides a comprehensive overview of how MSCs can mitigate the progression of NAFLD through various mechanisms, including modulation of glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. However, the review could benefit from a more detailed comparison of MSCs from different sources in treating NAFLD. While it is noted that the therapeutic properties of MSCs vary with their origin, more comprehensive studies comparing efficacy are needed. A more detailed analysis would be valuable. Additionally, discussions on integrated strategies, such as combining MSCs with pharmacotherapy, lifestyle modifications, gene therapy, cell therapy, and biomaterials, should be more extensive.

Given the current understanding of MSCs - regarding their classification, characteristics, and versatile roles in regenerative medicine - they hold great promise for treating NAFLD. Their ability to differentiate into various cell types and release factors that support tissue repair and regeneration makes them a compelling option for therapeutic interventions. Overall, MSCs are crucial for facilitating liver regeneration and repairing liver damage. Further research is required to address existing limitations and uncertainties. Future studies should focus on conducting more comprehensive comparisons of the efficacy of MSCs from different sources, exploring their detailed mechanisms of action, and performing well-designed clinical trials to validate the safety and efficacy of MSC-based therapies in combination with other treatment modalities. Additionally, efforts should be made to standardize isolation and culture protocols for MSCs to ensure the consistency and reliability in therapeutic effects. The development of new MSC-based therapies for liver ailments requires further research to elucidate the molecular mechanisms governing MSC - immune cell interactions. More studies and clinical validation are necessary to develop more effective and safer therapeutic strategies utilizing MSCs for NAFLD treatment.

FOOTNOTES

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LETTER TO THE EDITOR

Innovative mesenchymal stem cell treatments for fatty liver disease

Fei-Qiong Gao, Jia-Qi Zhu, Xu-Dong Feng

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Abstract

The incidence of non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) is increasing year by year due to changes in the contemporary environment and dietary structure, and is an important public health problem worldwide. There is an urgent need to continuously improve the understanding of their disease mechanisms and develop novel therapeutic strategies. Mesenchymal stem cells (MSCs) have shown promise as a potential therapeutic strategy in therapeutic studies of NAFLD and ALD. NAFLD and ALD have different triggers and their specific mechanisms of disease progression are different, but both involve disease processes such as hepatocellular steatosis and potential fibrosis, cirrhosis, and even hepatocellular carcinoma. MSCs have metabolic regulatory, anti-apoptotic, antioxidant, and immunomodulatory effects that together promote liver injury repair and functional recovery, and have demonstrated positive results in preclinical studies. This editorial is a continuum of Jiang *et al*'s review focusing on the advantages and limitations of MSCs and their derivatives as therapeutics for NAFLD and ALD. They detail how MSCs attenuate the progression of NAFLD by modulating molecular pathways involved in glucolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. Based on recent advances, we discuss MSCs and their derivatives as therapeutic strategies for NAFLD and ALD, providing useful information for their clinical application.

Key Words: Alcohol-associated liver disease; Non-alcoholic fatty liver disease; Mesenchymal stem cells; Cell therapy; Inflammation

Core Tip: Mesenchymal stem cells (MSCs) and their derivatives are a promising therapeutic approach for non-alcoholic fatty liver disease and alcohol-associated liver disease. MSCs, which come from diverse sources and are of low immunogenicity, can attenuate disease progression by modulating key molecular pathways, such as glycolipid metabolism, inflammation, oxidative stress, and fibrosis. In addition, derivatives of MSCs are also considered as a therapeutic strategy due to their ability to retain some of the beneficial effects of MSCs while reducing the risks inherent in cell therapy. However, further studies are needed to emphasize their important mechanistic role in liver injury repair. Refining protocols for the clinical application of MSCs under the prerequisite of a well-defined mechanistic understanding may allow utilizing the full benefits of MSCs in the treatment of liver disease to enhance liver reparability and provide new hope for the treatment of non-alcoholic fatty liver disease and alcohol-associated liver disease.

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TO THE EDITOR

Liver disease is responsible for 2 million deaths per year, about 4% of all deaths (1 in 25 deaths worldwide), and deaths are mainly attributed to complications of cirrhosis and hepatocellular carcinoma, with cirrhosis most commonly associated with viral hepatitis, and alcoholic and non-alcoholic fatty liver disease (NAFLD)[1]. The epidemiology and burden of NAFLD and alcohol-associated liver disease (ALD) are changing due to the rising prevalence of obesity and increased alcohol consumption. Age-standardized death rates for NAFLD-associated cirrhosis increased between 2012 and 2017, while age-standardized death rates for cirrhosis of other etiologies declined[2]. Although NAFLD and ALD share fatty liver/steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma, the two diseases are different in many ways, including risk factors, mechanisms of lipotoxicity, gut microbiome, mitochondrial dysfunction, and other pathogenic pathways[3]. Both NAFLD and ALD, as common chronic liver diseases, may eventually progress to end-stage liver disease, for which liver transplantation remains the only effective treatment but is limited by donor organ shortages, lifelong immunosuppression, and expensive treatment. Currently, cellular therapies have been investigated as a novel alternative treatment for chronic steatosis and inflammatory and fibrotic liver diseases.

Mesenchymal stem cells (MSCs) can be derived from a wide range of biological tissues, including bone marrow, adipose, umbilical cord, and placenta, and have a wide range of proliferative capacity and pluripotent biological properties[4]. They are promising for therapeutic applications due to their easy accessibility and proliferation in culture, genetic stability, low immunogenicity, and therapeutic properties in tissue repair and immunomodulation. MSCs treatment for NAFLD and ALD provides hepatoprotection, modulates inflammatory processes and angiogenesis, and may benefit liver disease by restoring liver function and reducing inflammation and fibrosis[5]. Furthermore, numerous preclinical studies have demonstrated that extracellular vesicles released from MSCs (MSC-EVs) have considerable potential in the treatment of liver diseases, and optimization of MSC-EVs culture conditions or modification of MSC-EVs further facilitates their development and clinical application in the treatment of liver diseases[6]. The minireview by Jiang *et al*[7] provides valuable insights into the advances in the study of MSCs therapy for the alleviation of NAFLD. Our editorial examines the in-depth mechanisms of MSCs and their derivatives in the treatment of NAFLD and ALD, with the aim of helping to understand and refine the protocols for the clinical application of MSCs and providing new hope for the treatment of NAFLD and ALD.

MSCs-based therapy and NAFLD

Numerous preclinical studies have demonstrated that MSCs from different sources have a role in attenuating obesity, glucose metabolism, hepatic steatosis, inflammation, and fibrosis, which is becoming increasingly prominent in cell therapy for NAFLD[8-10] (Table 1). This may also be realized by their effects on gut microecology[11]. Immunomodulation is an important factor influencing MSC transplantation, and it has been suggested that MSCs may show clinical value in the treatment of NAFLD/non-alcoholic steatohepatitis (NASH) through their ability to inhibit CD4+ T cell activation[12,13]. MSCs can also play a therapeutic role in ameliorating hepatic steatotoxicity and metabolic disturbances in the context of NAFLD by regulating endoplasmic reticulum stress and calcium homeostasis through sarco(endo)plasmic reticulum Ca(2+)-ATPase[14]. Hepatocyte growth factor was identified as a key functional cytokine secreted by menstrual-derived endometrial stem cells, which reduces hepatic Rnf186 expression and regulates glycolipid metabolism through the AMP-activated protein kinase/mechanistic target of rapamycin pathway to alleviate NAFLD [15]. Not only through the action of secreted factors, MSCs can also rescue dysfunctional mitochondria by transferring mitochondria, thus alleviating steatosis, liver function, and glucolipid metabolism disorders in NAFLD[16,17]. Due to the pluripotency of MSCs, their differentiated hepatocyte-like cells may serve as a source of replacement cells for primary hepatocytes, which, together with their anti-inflammatory and regeneration-promoting properties, could contribute to the

Table 1 Mesenchymal stem cell treatments for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and alcohol associated liver disease

Ref.	Cell source	Secretome	Model	Disease	Function and mechanism
Du *et al*[15]	MenSCs	HGF	Mouse	NAFLD	Rnf186 regulated glucose and lipid metabolism through the AMPK/mTOR pathway HGF decreased the expression of hepatic Rnf186
Wang *et al*[13]	Mouse BM-MSCs	-	Mouse	NAFLD	Suppressed the activation of CD4+ T cells
Hu *et al*[9]	Human UC-MSCs	-	Mouse	NASH	Alleviated obesity, glucose metabolism, hepatic steatosis, inflammation, and fibrosis Regulated lipid metabolism and the PPAR signaling pathway
Yang *et al*[11]	Human UC-MSCs	-	Mouse	NASH	Alleviated hepatic steatosis, inflammation, and fibrosis Reversed the microbiome and metabolome disorders
Li *et al*[14]	Rat BM-MSCs	-	Mouse/HepG2 cells	NAFLD	Regulation of ER stress and the calcium homeostasis *via* SERCA
Bi *et al*[16]	BM-MSCs	Mitochondria	Mouse/hepatocytes	NAFLD	Mitochondrial transfer from BMSCs rescued dysfunction mitochondria
Nickel *et al*[17]	Human BM-MSCs	Mitochondria	Mouse	NASH	Resolution of NASH in mouse livers involved the donation of human mitochondria to the mouse hepatocytes
Domingues *et al*[19]	Antioxidant-upregulated human AD-MSCs	-	Mouse	Diet-induced obese	Reduced oxidative stress post-antioxidant-upregulated MSC delivery, intraperitoneally, and reduced systemic inflammation and fat accumulation in the liver
Winkler *et al*[18]	Human BM-MSCs	-	Mouse	NASH	Transplantation of MSC-derived human hepatocyte-like cells corrects NASH in mice by restoring triglyceride depositions, reducing inflammation and augmenting the regenerative capacity of the liver
Cai *et al*[32]	BM-MSCs	-	Mouse	Chronic alcoholic hepatitis	Through the PI3K/NF-κB and PI3K/mTOR pathways Modulation of natural killer B cells and follicular helper T cells
Huai *et al*[37]	Human UC-MSCs	FGF21	Mouse	ALD	Enabled macrophages to exhibit anti-inflammatory inclination
Li *et al*[38]	Lysophosphatidic acid receptors and sphingosine-1-phosphate receptors-co-treated human AD-MSCs	-	Mouse	ALD	Ameliorated histological damage, oxidative stress, inflammation, fibrosis, and lipid metabolism dysfunction, and enhanced alcohol metabolizing enzyme activity
Ge *et al*[39]	BM-MSCs/BM-MSCs pre-activated with TLR3	-	Mouse	Chronic-binge alcohol	Protection against alcohol-induced intestinal and hepatic injury and immune dysfunction
Hernandez *et al*[40]	Human UC-MSCs	-	Mouse	Alcohol binge drinking	Activated stem cells resulted in marked improvement in survival and in recovery of hepatic chemistries
Chung *et al*[34]	Sk-MSCs	HGF	Mouse/human colonic Caco-2/tc7 cells	Alcoholic liver damage	Reduced inflammatory responses in the liver and gut

Wan *et al*[35]	BM-MSCs	TSG-6	Mouse	Alcoholic hepatitis	Secreted TSG-6 to inhibit STAT3 activation and to reduce liver injury
Wan *et al*[33]	BM-MSCs	-	Mouse	Alcoholic hepatitis	Inhibited hepatic neutrophil and macrophage infiltration, and alleviated oxidative stress

MenSCs: Menstrual-derived endometrial stem cells; HGF: Hepatocyte growth factor; NAFLD: Non-alcoholic fatty liver disease; BM-MSCs: Bone marrow mesenchymal stem cells; UC-MSCs: Umbilical cord mesenchymal stem cells; NASH: Non-alcoholic steatohepatitis; AD-MSCs: Adipose-derived mesenchymal stem cells; ALD: Alcohol associated liver disease; Sk-MSCs: Skeletal muscle satellite cell-derived mesenchymal stem cells; SERCA: Sarco(endo)plasmic reticulum Ca(2+)-ATPase; AMPK: AMP-activated protein kinase; PI3K: Phosphoinositide 3-kinase; mTOR: Mechanistic target of rapamycin; NF-κB: nuclear factor kappa B; TSG-6: Tumor necrosis factor-stimulated gene-6; STAT3: Signal transducer and activator of transcription 3; FGF21: Fibroblast growth factor 21; TLR3: Toll-like receptor 3; PPAR: Peroxisome proliferator-activated receptor; ER: Endoplasmic reticulum; BMSC: Bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell.

recovery of NASH-injured liver after transplantation[18]. MSCs with different special pretreatment protocols may play similar beneficial roles in the treatment of different kinds of diseases. For example, antioxidant-up-regulated modified MSCs play an important role in reducing oxidative stress, improving glucose tolerance, reducing systemic inflammation, and ameliorating fatty liver disease[19]. MSC exosomes also showed similar enhancement effects after pretreatment, *e.g.*, curcumin[20] pretreatment and pan-peroxisome proliferator-activated receptor agonist induction[21].

Small extracellular vesicles derived from MSCs have shown promise in animal models for the treatment of NAFLD, which has led to consideration of their clinical translation[22,23] (Table 2). Kang *et al*[24] demonstrated that human umbilical cord MSCs exosomes (hUC-MSC-Exos) attenuated hepatocellular steatosis, reduced inflammatory macrophages as well as tumor necrosis factor-α and interleukin-6 to inhibit hepatic inflammatory response, and suppressed oxidative stress to alleviate NASH through the nuclear factor erythroid 2-related factor 2/NAD(P)H quinone oxidoreductase-1 antioxidant signaling pathway. In addition, hUC-MSC-Exos can prevent NAFLD by modulating lipid homeostasis through transferring calcium/calmodulin-dependent protein kinase 1 to improve lipid accumulation, inhibit fatty acid synthesis, and enhance fatty acid oxidation[25]. In addition, MSC-Exos are rich in nucleic acids that play important roles in inhibiting lipid accumulation, reactive oxygen species generation, inflammation, and liver fibrosis, which provide potential therapeutic value for NAFLD treatment, such as miR-24-3p[26], miR-223-3p[27], miR-627-5p[28], and miR-96-5p [29]. MSCs not only promote mitochondrial homeostasis in hepatocytes through mitochondrial transfer. Furthermore, it was shown that RNF31 transport *via* MSCs-derived small extracellular vesicles has a substantial impact on the regulation of hepatocyte mitochondrial homeostasis, hepatic steatosis, and recovery of liver function[30]. MSCs release a large number of molecules in conditioned medium, which may have similar beneficial effects in ameliorating NAFLD without pitfalls such as cellular obstruction, and have the potential for clinical application[31]. Clinical trials regarding MSCs therapy for NAFLD are also being conducted progressively and are expected to provide new therapeutic options for clinical application in patients[8].

MSCs-based therapy and ALD

Despite numerous studies dedicated to demonstrating the therapeutic potential of MSCs in the management of acute and chronic liver diseases, the field of utilizing MSCs in the treatment of ALD has not yet been sufficiently reported in the scientific literature (Table 1). Cai *et al*[32] previously reported that the combination of bone marrow-derived MSCs (BM-MSCs) and *Lactobacillus plumosus* culture supernatant may ameliorate the symptoms of alcoholic hepatitis through modulation of the phosphoinositide 3-kinase/nuclear factor kappa B and phosphoinositide 3-kinase/mechanistic target of rapamycin pathways, as well as modulation of natural killer B cells and follicular helper T cells. MSCs have been used to treat many inflammatory diseases, and studies have shown that MSCs are effective in treating alcoholic hepatitis through their ability to inhibit hepatic neutrophil and macrophage infiltration and attenuate oxidative stress[33]. Skeletal muscle satellite cell-derived MSCs exert anti-inflammatory effects through the secretion of prostaglandin E2 and hepatocyte growth factor, which may attenuate alcoholic liver injury by decreasing the inflammatory response in the liver and intestine[34]. Tumor necrosis factor-stimulated gene-6 secreted by BM-MSCs is able to inhibit signal transducer and activator of transcription 3 activation, thereby reducing liver injury and treating alcoholic hepatitis[35]. Application of tumor necrosis factor-stimulated gene-6 alone attenuates alcohol-induced liver injury and fibrosis by blocking the cleavage of CD44 to form the CD44 intracellular domain[36]. Pretreated MSCs likewise had enhanced therapeutic effects on ALD, and fibroblast growth factor 21-overexpressing MSCs promoted the immunomodulatory function of MSCs on macrophages through metabolic regulation of oxidative phosphorylation, causing macrophages to exhibit anti-inflammatory tendencies and thus alleviating ALD[37]. Lysophosphatidic acid receptor and sphingosine-1-phosphate receptor-co-treated human adipose-derived MSCs exhibit significant therapeutic efficacy that could enhance their efficacy in the future treatment of ALD[38]. Toll-like receptor 3-preactivated BM-MSCs can be used to protect against alcohol-induced intestinal and hepatic injury[39]. Activated hUC-MSCs significantly improved hepatocyte survival and recovery of hepatocyte chemical function compared with non-activated stem cells, which has important clinical applications[40].

BM-MSCs transplantation has been recognized as an effective treatment for liver cirrhosis, and there are clinical trials investigating the efficacy and safety of autologous BM-MSCs transplantation for alcoholic cirrhosis[41,42]. Chronic high intake of ethanol can lead to a variety of metabolic changes in the body and increased levels of ethanol and its metabolites in the body's microenvironment. It has been shown that ethanol inhibits BM-MSCs-mediated hepatocyte renewal in rats,

Table 2 Mesenchymal stem cell derivatives for treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

Ref.	Cell source	Secretome	Model	Disease	Function and mechanism
Kang *et al*[24]	Human UC-MSC-EV	-	Mouse/HepG2 and AML12 cells	NASH	Nrf2/NQO-1 antioxidant signaling pathway
Yang *et al*[25]	Human UC-MSC-EV	CAMKK1	Mouse/hepatic cells	NAFLD	CAMKK1-mediated lipid homoeostasis regulation
Chen *et al*[30]	MSC-sEV	RNF31	Mouse	NAFLD	Regulation of mitochondrial homeostasis
Du *et al*[26]	Human UC-MSC-Exo	MiRNA-24-3p	Mouse/hepatocytes	NAFLD	MiR-24-3p directly targeted Kelch-like ECH-associated protein 1, and suppressed its expression Restrained lipid accumulation, ROS generation, and inflammation
Niu *et al*[27]	AD-MSC-EV	MiRNA-223-3p	Mouse/hepatocytes	NAFLD	MiR-223-3p displayed suppressive effects on lipid accumulation and liver fibrosis through E2F1 inhibition
Cheng *et al*[28]	Human UC-MSC-Exo	MiRNA-627-5p	Rat/L-02 cells	NAFLD	MiR-627-5p improved glucose and lipid metabolism and alleviated liver damage by repressing FTO expression
El-Derany *et al*[29]	BM-MSC-Exo	MiRNA-96-5p	Mouse	NASH	Caspase-2 signaling inhibition
Tawfeek and Kasem[20]	Curcumin-preconditioned MSC-Exo	-	Mouse/HepG2 cells	NASH	Regulated inflammatory, oxidative stress, and mitochondrial-dependent apoptosis-associated *ASK-JNK-BAX* genes
Kim *et al*[21]	Pan-peroxisome proliferator-activated receptor agonist-primed induced MSC-EV	-	Mouse	NASH	Reduced steatotic changes and ameliorated ER stress and mitochondiral oxidative stress induced by inflammation
Zhang *et al*[23]	MSC-sEV	-	Mouse	NASH	Polarized pro-fibrotic M2 macrophages without exacerbating liver fibrosis
Yang *et al*[31]	MSCs conditional medium	-	Mouse/L-02 cells	NAFLD	Improved mitochondrial function and alleviated inflammation and apoptosis by regulating SIRT1

UC-MSC-EV: Umbilical cord mesenchymal stem cells extracellular vesicle; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; MSC-sEV: Mesenchymal stem cells small extracellular vesicle; UC-MSC-Exo: Umbilical cord mesenchymal stem cells exosome; AD-MSC-EV: Adipose-derived mesenchymal stem cells extracellular vesicle; BM-MSC-Exo: Bone marrow mesenchymal stem cells exosome; Nrf2: Nuclear factor erythroid 2-related factor 2; NQO-1: NAD(P)H quinone oxidoreductase-1; CAMKK1: Calcium/calmodulin-dependent protein kinase 1; ROS: Reactive oxygen species; MSC: Mesenchymal stem cell.

which may affect the clinical application of MSCs for the treatment of ALD[43], and more research should be invested in exploring the in-depth mechanisms and solutions.

CONCLUSION

NAFLD and ALD are common chronic diseases with a poor prognosis. Finding treatments for these diseases can improve the prognosis and quality of life of patients. Stem cell transplantation is an emerging therapy for the treatment of acute and chronic liver diseases. Both MSCs and their derivatives are attractive therapeutic tools that have been widely explored in preclinical and clinical studies. The incidence of NAFLD and ALD is increasing every year and constantly threatening human health. MSCs secrete molecules and EVs that are considered to have potential as therapeutic agents for NFALD and ALD. However, data from preclinical studies of MSC-derived products for the treatment of animal models of ALD are limited. In addition, a large amount of research data is needed to support the current development of clinical applications of MSCs for NAFLD and ALD, including the optimal therapeutic dose, standardized pretreatment modalities, and therapeutic infusion routes. According to the review by Jiang *et al*[7], MSCs are a promising therapeutic candidate for NAFLD. However, further studies are needed to investigate the relationship between the pathological

events that occur during the development of NAFLD and ALD and the cellular and molecular mechanisms associated with the therapeutic effects of MSCs. In conclusion, MSCs are clearly a promising and attractive resource for the development of liver disease therapies, and further comprehensive studies to develop safer and more effective strategies for the treatment of NAFLD and ALD would be beneficial to realize their therapeutic potential.

FOOTNOTES

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