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The rise of exosome-mediated mechanisms in MSC therapy

Weihua Liu^{1†}, Sheng Chen^{2†}, Yuan Wang² and Wei Gong^{1,3*}

Abstract

Background Graft-versus-host disease (GVHD) remains a critical complication following allogeneic hematopoietic cell transplantation. Mesenchymal stromal cells (MSCs) have demonstrated promising immunomodulatory effects in mitigating GVHD. Despite the growing body of research, a comprehensive bibliometric evaluation of MSCs in GVHD is still lacking.

Objective To perform a bibliometric analysis of global research on MSC-based therapies for GVHD using Citespace and VOSViewer, with the aim of mapping publication trends, collaboration networks, and emerging research hotspots.

Methods Publications from 2010 to 2023 were retrieved from the Web of Science using targeted search strategies. Data analysis was conducted using Citespace, VOSViewer, and the R package “bibliometrix” to construct co-authorship, co-citation, and keyword networks. Visualization maps were generated to illustrate publication trends, geographic distributions, and thematic evolution in MSC-GVHD research.

Results A total of 875 relevant publications from 58 countries were identified. The analysis revealed a substantial increase in research output over the past decade, with a notable focus on extracellular vesicle and exosome-mediated mechanisms in MSC therapy. Prominent collaboration networks were observed among leading countries, notably between the United States and China, and key authors and institutions were delineated. Emerging hotspots and trends in MSC-GVHD research were identified, underscoring areas of potential translational significance.

Conclusion This bibliometric study provides a comprehensive overview of the evolving landscape of MSC research in GVHD. The findings highlight significant global trends and collaboration patterns that can inform both future basic research and clinical translation. These insights are critical for guiding further exploration and optimization of MSC-based therapeutic strategies in GVHD.

Keywords Mesenchymal stromal cells, Graft-versus-host disease, Bibliometric analysis, Citespace, VOSViewer, Translational medicine

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Introduction

Graft-versus-host disease (GVHD) is a common and severe immunological complication following allogeneic hematopoietic cell transplantation (HCT), with an incidence of 40–60% and a mortality rate reaching up to 15%, significantly impairing patients' quality of life [1, 2]. GVHD manifests in various forms, primarily as skin inflammation, persistent diarrhea, hepatobiliary disorders, pulmonary fibrosis, and musculoskeletal injuries [3, 4]. Moreover, GVHD is closely linked to long-term non-relapse mortality, with reported 5-year and 12-year rates of 22% and 40%, respectively; HCT itself also elevates the risk of secondary cancers, with GVHD patients facing a 2.4-fold increased risk [1, 5]. Human leukocyte antigen (HLA) mismatch is recognized as a key determinant in the development of GVHD, while other contributing factors include advanced recipient age, gender disparities between donor and recipient, multiparity of the donor, graft source, and the application of total body irradiation [6, 7].

Mesenchymal stromal cells (MSCs), which can be isolated from bone marrow, adipose tissue, and neonatal tissues, exhibit remarkable proliferative, homing, and immunomodulatory capabilities, making them promising candidates for treating conditions such as osteonecrosis, retinitis pigmentosa, ischemic cardiomyopathy, acute kidney injury, liver cirrhosis, Crohn's disease, systemic lupus erythematosus, and GVHD [8]. MSCs isolated in vitro are not homogeneous stem cell populations, and they lack the biological functions of stem cells. The International Society for Cellular Therapy has recommended that these spindle-shaped, plastic-adherent cells be termed, "mesenchymal stromal cells" [9, 10].

In the treatment of GVHD, MSCs function by inhibiting T-cell proliferation and activity, inducing the generation of regulatory CD4⁺CD25⁺T cells, and suppressing dendritic cell activation [11]. Despite a rapid increase in research on MSC-based therapies for GVHD over the past two decades, a systematic bibliometric analysis that summarizes recent advances, elucidates international collaboration networks, and predicts future trends is still lacking. To address this gap, the present study employs bibliometric methods using tools such as Citespace and VOSviewer to comprehensively analyze the research structure and emerging hotspots in this field, ultimately providing robust guidance for the clinical application of MSCs in GVHD and future research directions.

Materials and methods

Data retrieval and collection

For this bibliometric analysis, data were retrieved from the Web of Science (WoS), a premier database comprising 171 million records, over 34,000 journal indexes, 1.89 billion cited references, and archival coverage

spanning more than 119 years [12]. In November 2024, a comprehensive literature search was conducted on WoS using the query: (TS = ("mesenchymal stem cells") AND TS = ("graft-versus-host disease")). We extracted key metadata for each publication, including the title, abstract, authors, affiliations, country/region, journal, keywords, and references. Only original research articles and review papers published in English were included. Duplicate publications have been removed. The detailed selection process is presented in Fig. 1.

Data analysis

Citespace, a bibliometric visualization tool developed by Professor Chaomei Chen, was employed to construct networks that depict underlying entities and their inter-relationships from representative datasets in the field [13–16]. Using Citespace, we conducted co-authorship analysis, citation analysis, dual-map overlay visualization, and citation burst detection. Additionally, VOSviewer, developed by Leiden University, was utilized to create and explore visual maps based on network data. Specifically, VOSviewer facilitated the analysis and visualization of networks involving countries and institutions, journals and co-cited journals, authors and co-cited authors, as well as keyword co-occurrences. In these maps, nodes represent entities (e.g., countries, institutions, journals, authors) with sizes proportional to the frequency of occurrence, and the thickness of the connecting lines indicates the strength of collaboration or co-citation [17, 18]. Furthermore, the R package "bibliometrix" (<https://www.bibliometrix.org>) was used to perform thematic evolution analysis and to construct a global distribution network of MSC-GVHD publications. Data management and supplementary analyses were performed using Microsoft Office Excel 2019.

Results

Publication volume analysis

Based on our search strategy, 875 publications on MSCs in GVHD were identified over the past decade. As shown in Fig. 2, research in this field has been extensive, with a steady increase in publications from 2010 to 2014. Notably, fluctuations were observed in 2015, 2017, and 2022, while the period from 2017 to 2021 also demonstrated a rising trend, reaching an annual peak of up to 73 publications.

Analysis of countries and institutions

The 875 publications originated from 58 countries and 1,418 institutions. As detailed in Table 1, the top ten countries span North America, Asia, and Europe—with three from Asia and five from Europe. The United States led with 216 publications (18.3%), followed by China (197, 16.7%), Germany (93, 7.8%), and Italy (65,

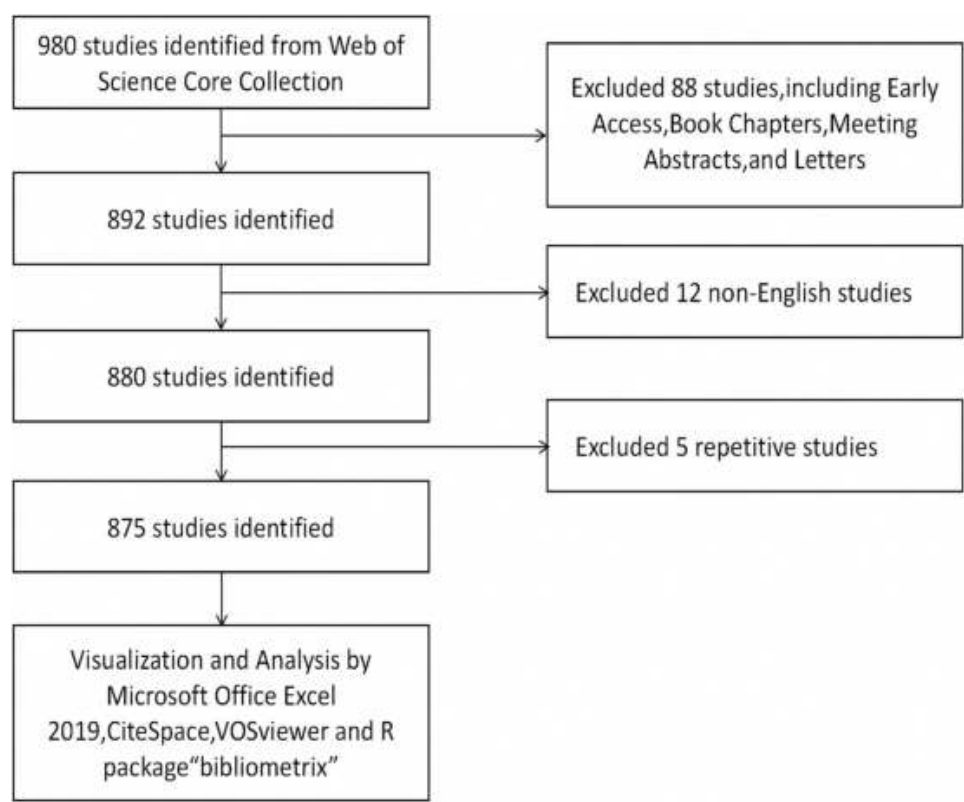


Fig. 1 Publications screening flowchart

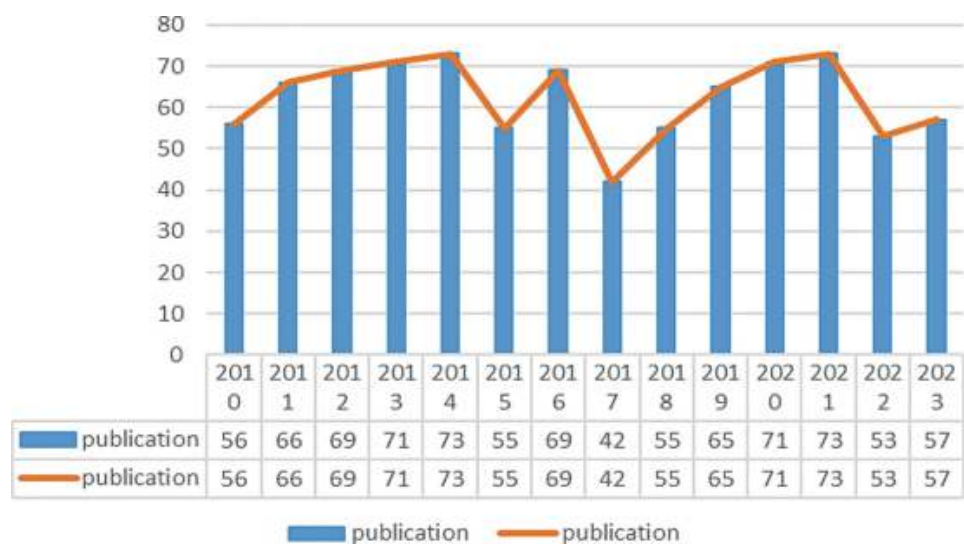


Fig. 2 Annual output of research of MSC in GVHD

5.5%). Combined, the United States and China contributed nearly one-third (35%) of the total output. After filtering for countries with at least five publications, a collaborative network was constructed (Fig. 3), which reveals robust international cooperation—evidenced by strong collaborative links between China and the United States, the United Kingdom, Germany, and Japan, as well as between the United States and Germany, Korea, the

Netherlands, and Sweden. Furthermore, analysis of the top ten institutions (from six countries) indicated that Chinese institutions were most prolific, with Karolinska Institute (41 publications, 1.91%), Southern Medical University (24, 1.12%), and Sun Yat-sen University (23, 1.07%) ranking highest. A collaboration network of 68 institutions (each with at least six publications) was visualized (Fig. 4), which highlights that although Sun Yat-sen

Table 1 Top 10 countries and institutions on research of MSCs in GVHD

Rank	Country	Counts	Institution	Counts
1	USA(North America)	216(18.3%)	Karolinska Institute(Sweden)	41(1.91%)
2	China(Asia)	197(16.7%)	Southern Medical University(China)	24(1.12%)
3	Germany(Europe)	93(7.8%)	Sun Yat Sen University(China)	23(1.07%)
4	Italy(Europe)	65(5.5%)	Karolinska University Hospital(Sweden)	22(1.02%)
5	England(Europe)	56(4.7%)	Case Western Reserve University(USA)	18(0.84%)
6	Japan(Asia)	51(4.3%)	Leiden University(Netherlands)	16(0.74%)
7	Sweden(Europe)	48(4.1%)	Emory University(USA)	15(0.69%)
8	Netherlands(Europe)	38(3.2%)	Catholic University Korea(South Korea)	13(0.60%)
9	South Korea(Asia)	35(2.9%)	Chinese Academy Medical Science(China)	13(0.60%)
10	Canada(North America)	34(2.8%)	Hannover Medical School(Germany)	12(0.56%)

University began its research earlier, its publication output was lower than that of Southern Medical University, and that the top two institutions did not exhibit close inter-institutional collaboration.

Journals and co-cited journals analysis

Publications on MSCs in GVHD were distributed across 316 journals. *Frontiers in Immunology* published the most articles (49, 5.6%), followed by *Cytotherapy* (42, 4.8%), *Biology of Blood and Marrow Transplantation* (36, 4.1%), and *Stem Cell Research & Therapy* (31, 3.5%). Among the top 15 journals in terms of publication volume, *Blood* had the highest impact factor (IF=21), followed by *Frontiers in Immunology* (IF=5.7). By selecting journals with a minimum of five publications, a journal network was generated (Fig. 5A), which demonstrated highly active citation relationships among the top three journals. Table 2 shows that among the top 15 co-cited journals, nine received over 1,000 citations, with *Blood* leading at 6,614 co-citations, followed by *Biology of Blood and Marrow Transplantation* (2,817), *Stem Cells* (2,469), and *Bone Marrow Transplantation* (2,018). Additionally, *Lancet* (IF=98.4) and *New England Journal of Medicine* (IF=96.2) were the highest impact co-cited journals. A co-citation network, constructed for journals with at least 70 co-citations, is presented in Fig. 5B, revealing strong links between *Blood* and journals such as *Biology Blood Marrow Transplantation*, *Bone Marrow Transplantation*, and *Stem Cells*. An overlay dual-map (Fig. 6) further illustrates the citation pathways: articles in *Molecular/Biology/Genetics* journals are mainly cited by literature in *Molecular/Biology/Immunology* and *Medicine/Medical/Clinical* journals, while those in *Health/Nursing/Medicine* journals are primarily referenced by *Molecular/Biology/Immunology* journals.

Authors and co-cited authors analysis

A total of 5,008 authors contributed to the field of MSCs in GVHD. The top six authors each published at least 10 articles (Table 3). A collaboration network, constructed from authors with a minimum of five publications, is

shown in Fig. 7A. Olle Ringdén emerged as the most prolific author with 25 publications between 2010 and 2023, and he demonstrated extensive collaboration with Le Blanc K, whereas Liu Qifa did not collaborate with these key authors. Among 22,607 co-cited authors, 10 were cited more than 200 times (Table 3), with Le Blanc K receiving the highest co-citations (740), followed by Olle Ringdén (325). A co-citation network of authors with at least 50 co-citations (Fig. 7B) illustrates active collaboration among co-cited authors, notably among Le Blanc K, Olle Ringdén, Krampera M, and Dominici M.

Co-cited references analysis

Over the past 13 years, a total of 32,542 co-cited references related to MSCs in GVHD were identified. Among the top ten co-cited references (Table 4), each was cited at least 122 times, with two references exceeding 300 co-citations. We selected references with co-citation more than or equal to 40 for the construction of the co-citation network map (Fig. 8). According to Fig. 8, “leblanc k, 2008, lancet” shows active co-cited relationships with “dominici m, 2006, cytotherapy” and “aggarwal s, 2005, blood”, etc.

Citation burst analysis

Citation burst analysis identifies references that experienced a surge in citations over a short period. Citespace detected 11 references with significant citation bursts (Fig. 9), where each bar represents a year and red bars denote strong bursts. The strongest burst (strength=51.74) was observed for the reference titled “Mesenchymal stem cells for treatment of steroid resistant, severe, acute graft-versus-host disease: a phase II study” by Le Blanc K et al., with a burst period from 2010 to 2013. The second strongest burst (strength=20.98) was noted for “Mesenchymal stem cells for treatment of therapy resistant graft-versus-host disease” by Olle Ringdén et al., with a burst period from 2010 to 2011. Overall, burst strengths ranged from 13.68 to 51.74, with durations spanning 2 to 6 years. Table 5 summarizes the key

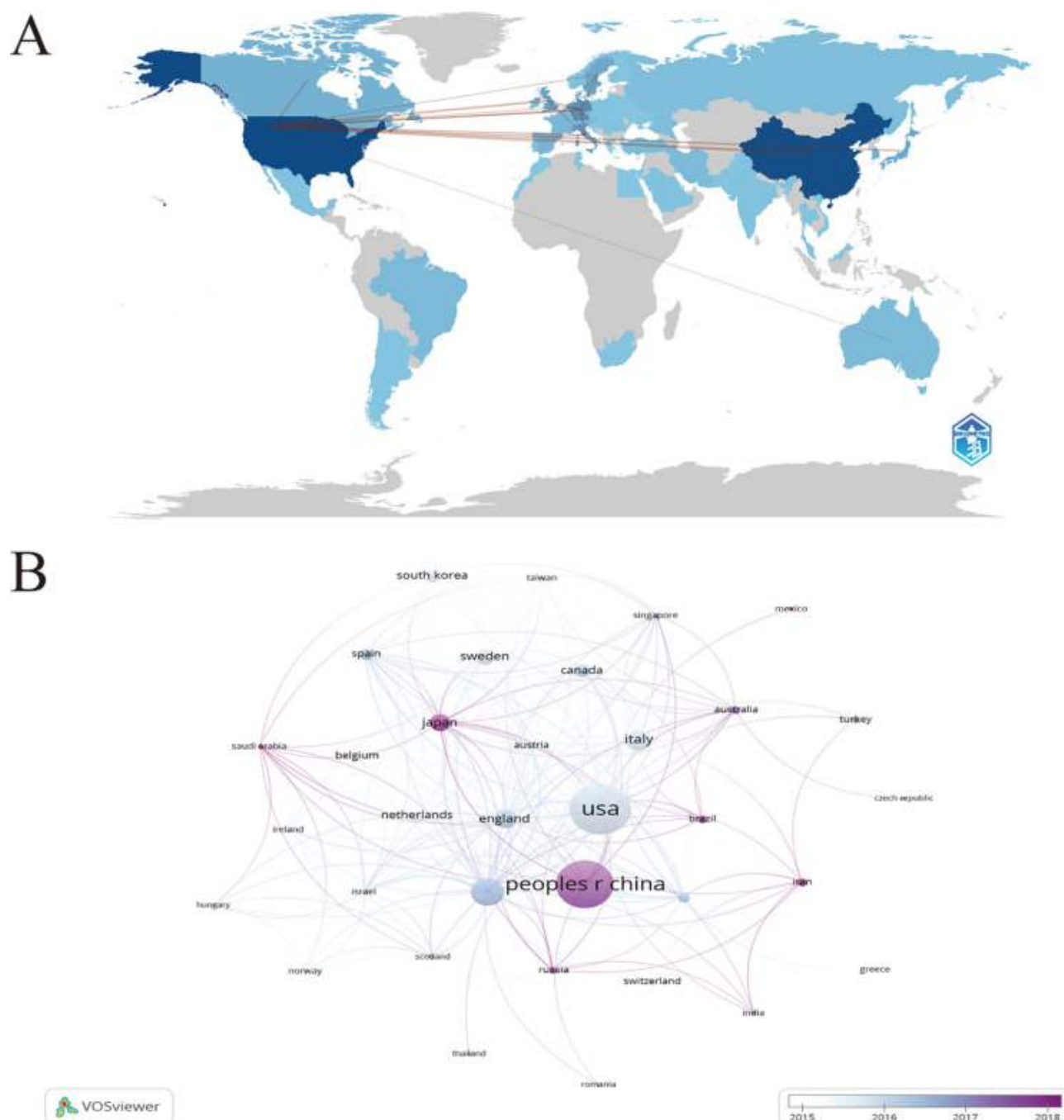


Fig. 3 The geographical distribution (A) and visualization of countries (B) on research of MSC in GVHD

research content of these 11 references in the order presented in Fig. 9.

Hotspots and frontiers

Keyword co-occurrence analysis revealed the research hotspots within MSCs in GVHD. Table 6 lists the top 20 high-frequency keywords, including “hematopoietic stem cell transplantation” and “immunomodulation,” each appearing over 60 times, which underscores the main

research directions in this field. Keywords appearing at least six times were filtered and subjected to clustering analysis using VOSviewer (Fig. 10A), resulting in six distinct clusters. The red cluster includes terms such as “extracellular vesicles,” “exosomes,” “regenerative medicine,” and “cell therapy.” The green cluster comprises keywords such as “transplantation,” “hematopoietic stem cells,” “cord blood,” and “NK cells.” The yellow cluster features terms like “immunosuppression,” “bone marrow,”

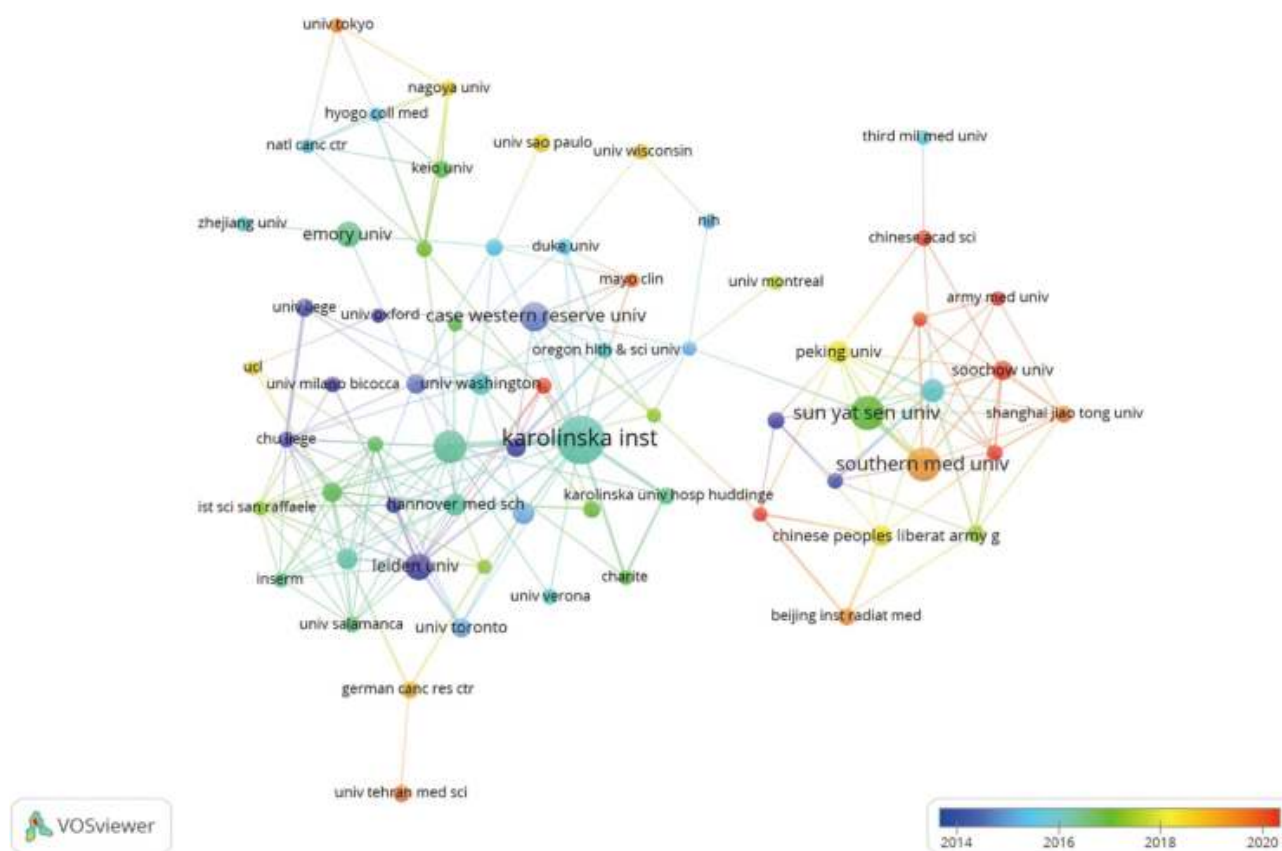


Fig. 4 The visualization of institutions on research of MSC in GVHD

“immune tolerance,” and “immunotherapy.” The dark blue cluster includes keywords related to “hematopoietic stem cell transplantation,” “children,” “allogeneic hematopoietic cells,” and “steroids,” while the light blue cluster focuses on “immunomodulation” and “cell therapy.” The purple cluster comprises “cord,” “T cells,” and “placenta.” Moreover, keyword trend analysis (Fig. 10B) indicates that since 2016, there has been an increasing focus on the pathogenesis and therapeutic potential of MSCs in GVHD, with primary keywords such as “hematopoietic stem cell transplantation,” “immunomodulation,” and “cell therapy.” In addition, the continued prominence of MSC-related keywords in 2021–2022, along with emerging terms such as “exosomes,” “PD-L1,” and “bone marrow niche,” suggests these may represent the current research frontiers.

Discussion

Between 2010 and 2023, the annual publication count consistently exceeded 40, underscoring that research on MSC-based therapies for GVHD has long been a hotspot. This sustained interest has laid a robust foundation for the clinical application of MSCs in treating GVHD.

China and the United States are the leading countries in MSC research for GVHD, with the United States ranking

first. Among the top ten research institutions, those from China and the United States account for 30% and 20% of the total, respectively. Notably, strong collaborative ties were observed among China, the United States, and Italy, while Italy also actively cooperates with Germany, the United Kingdom, and Sweden. At the institutional level, close collaboration was evident among entities such as Sun Yat-sen University and Southern Medical University. Moreover, the Karolinska Institute not only published the highest number of articles but also maintained extensive inter-institutional collaborations, which is beneficial for long-term academic development. However, the overall breadth and intensity of collaboration among institutions remain suboptimal; for instance, despite high publication outputs, Sun Yat-sen University and Southern Medical University exhibited only limited cooperation with international counterparts. This gap in inter-institutional collaboration may hinder the field’s progress, and therefore, enhanced global collaboration and exchange are strongly recommended to further advance MSC research in GVHD.

The majority of studies on MSCs in GVHD have been published in *Frontiers in Immunology* (IF=5.7, Q1), indicating its status as the most popular journal in this field. Among the top journals, *Blood* (IF=21, Q1) ranks

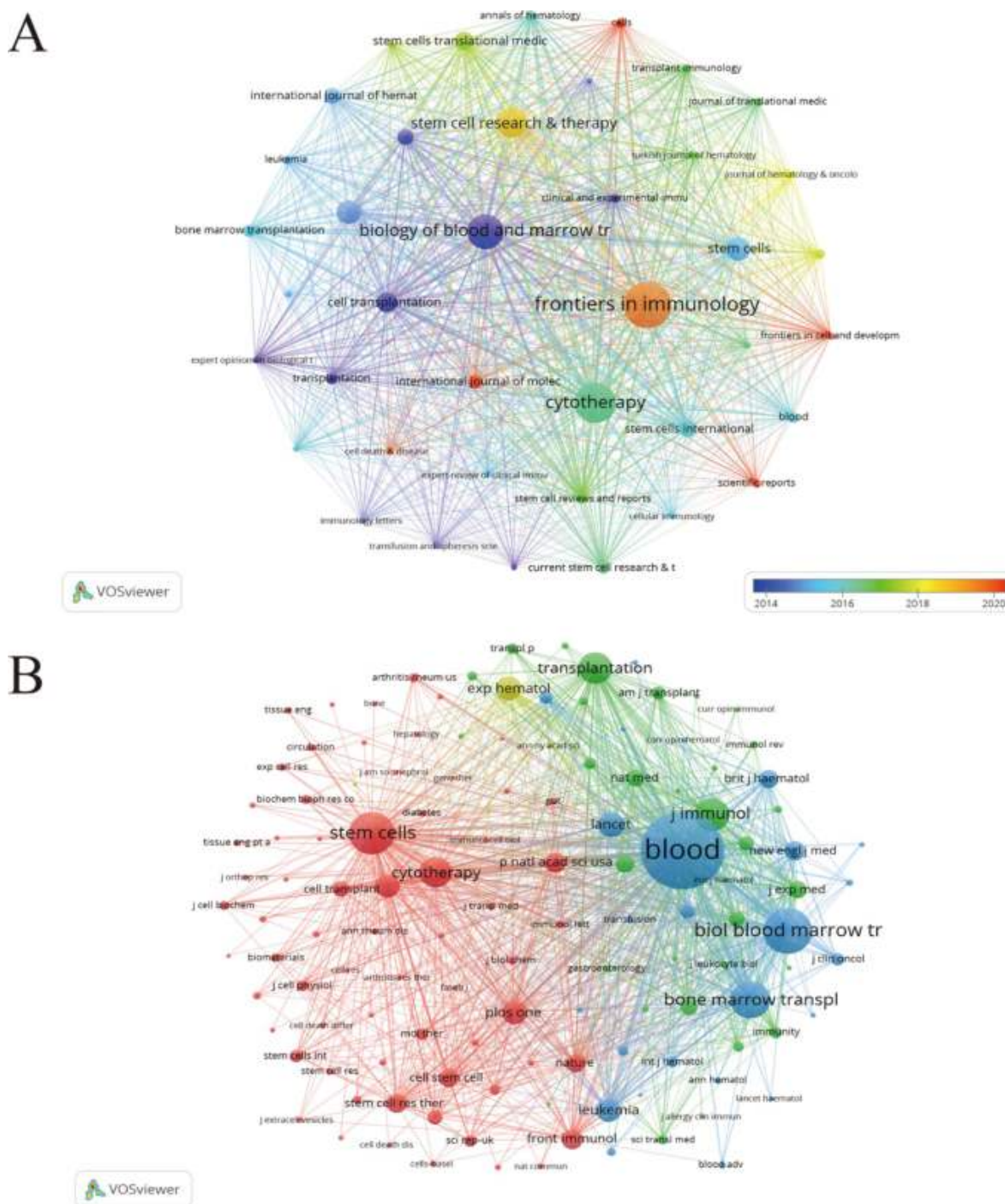


Fig. 5 The visualization of journals (A) and co-cited journals (B) on research of MSC in GVHD

highest, followed by *Frontiers in Immunology*. The co-cited journals are predominantly high-impact Q1 publications, which serve as a solid foundation for research in MSC-based GVHD therapies. Additionally, the concentration of MSC-GVHD studies in molecular biology, biology, and immunology journals—with only a few appearing in clinical journals—suggests that most research remains in the preclinical stage.

Regarding authorship, both Olle Ringdén and Le Blanc K have each published more than 15 articles. As early as 2006, Olle Ringdén and colleagues proposed that MSCs show great promise in treating severe steroid-resistant acute GVHD [19, 20]. They demonstrated that both undifferentiated and differentiated embryonic MSCs do not trigger allo-reactive lymphocyte proliferation and noted that MSCs have already been approved for treating

Table 2 Top 15 journals and co-cited journals for research of MSCs in GVHD

Rank	Journal	Count	IF	Q	Co-cited Journal	Co-citation	IF	Q
1	Frontiers in Immunology	49 (5.6%)	5.7	1	Blood	6614	21	1
2	Cytotherapy	42 (4.8%)	4.5	1	Biology Blood Marrow Transplantation	2817	4.3	1
3	Biology of Blood and Marrow Transplantation	36 (4.1%)	4.3	1	Stem Cells	2469	4	1
4	Stem Cell Research & Therapy	31 (3.5%)	1.2	4	Bone Marrow Transplantation	2018	4.5	1
5	Stem Cells and Development	23 (2.6%)	2.5	2	Journal Immunology	1664		
6	stem cells	23 (2.6%)	4	1	Transplantation	1546	5.3	1
7	Cell Transplantation	19 (2.2%)	3.2	2	Cytotherapy	1514	4.5	1
8	Stem Cells Translational Medicine	17 (1.9%)	5.4	1	Lancet	1055	98.4	1
9	Stem Cells International	15 (1.7%)	3.8	2	Experimental Hematology	1020	2.5	2
10	Plos One	14 (1.6%)	2.9	1	Plos One	961	2.9	1
11	International Journal of Hematology	14 (1.6%)	1.7	3	Leukemia	958	12.8	1
12	International Journal of Molecular Sciences	12 (1.4%)	4.9	1	Stem Cells Development	938	2.5	2
13	Bone Marrow Transplantation	11 (1.3%)	4.5	1	Frontiers in Immunology	772	5.7	1
14	Transplantation	10 (1.1%)	5.3	1	Proceedings National Academy Sciences USA	755	9.4	1
15	Blood	9 (1.0%)	21	1	New England Journal Medicine	715	96.2	1

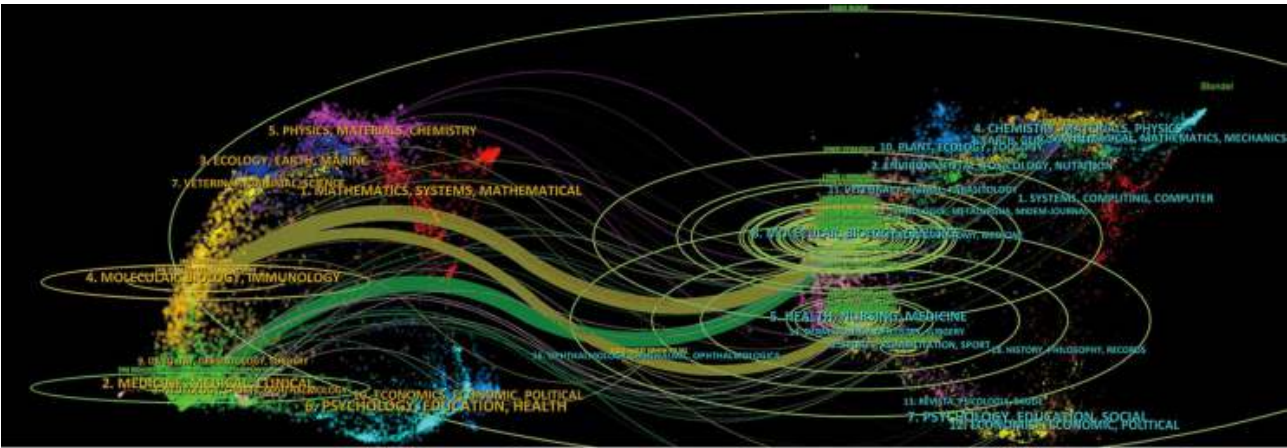


Fig. 6 The dual-map overlay of journals on research of MSC in GVHD

Table 3 Top 10 authors and co-cited authors on research of MSCs in GVHD

Rank	authors	count	Co-Cited Authors	citations
1	Ringden Olle	25	Le Blanc K	740
2	Le Blanc, Katarina	17	Leblanc K	393
3	Liu Qifa	13	Ringdén O	325
4	Sadeghi Behnam	11	Krampera M	273
5	Galipeau Jacques	11	Dominici M	254
6	Gustafsson Britt	10	Aggarwal S	228
7	Remberger Mats	9	Pittenger Mf	224
8	Bader Peter	9	Friedenstein Aj	206
9	Cho Seok-goo	9	Kebraie P	205
10	Kim Nayoun	9	Bernardo Me	202

acute GVHD in Japan, as well as for pediatric patients in Canada and New Zealand [21–23]. Furthermore, MSCs are known to suppress T-cell responses induced by allo-antigens; Olle Ringdén’s team also found that virus-specific T-cell effector functions remain preserved after MSC infusion, a finding with significant implications

for MSC immunotherapy in GVHD [24]. More recently, Olle Ringdén and colleagues have highlighted the potential of decidual MSCs as a promising new cell therapy for steroid-resistant acute GVHD [25]. Placenta-derived decidual stromal cells exhibit enhanced immunosuppressive effects—not only through systemic paracrine mechanisms but also by selectively targeting local T cells in affected tissues [26–30]. Their clinical report on six pediatric cases showed that decidual MSC treatment yielded complete remission in four patients and partial remission in two, with a 5-year survival rate of 67% [31]. In addition, placenta-derived decidual MSCs have been found to improve oxygenation, reduce inflammatory cytokine levels, and clear pulmonary infiltrates in COVID-19 patients [32], and early passage MSCs have been shown to improve survival in GVHD patients [33]. Le Blanc K has also published several high-impact studies; for example, a review in Nature Reviews Immunology emphasized that both adaptive and innate immune responses are crucial in sustaining alloimmunity, and that innate

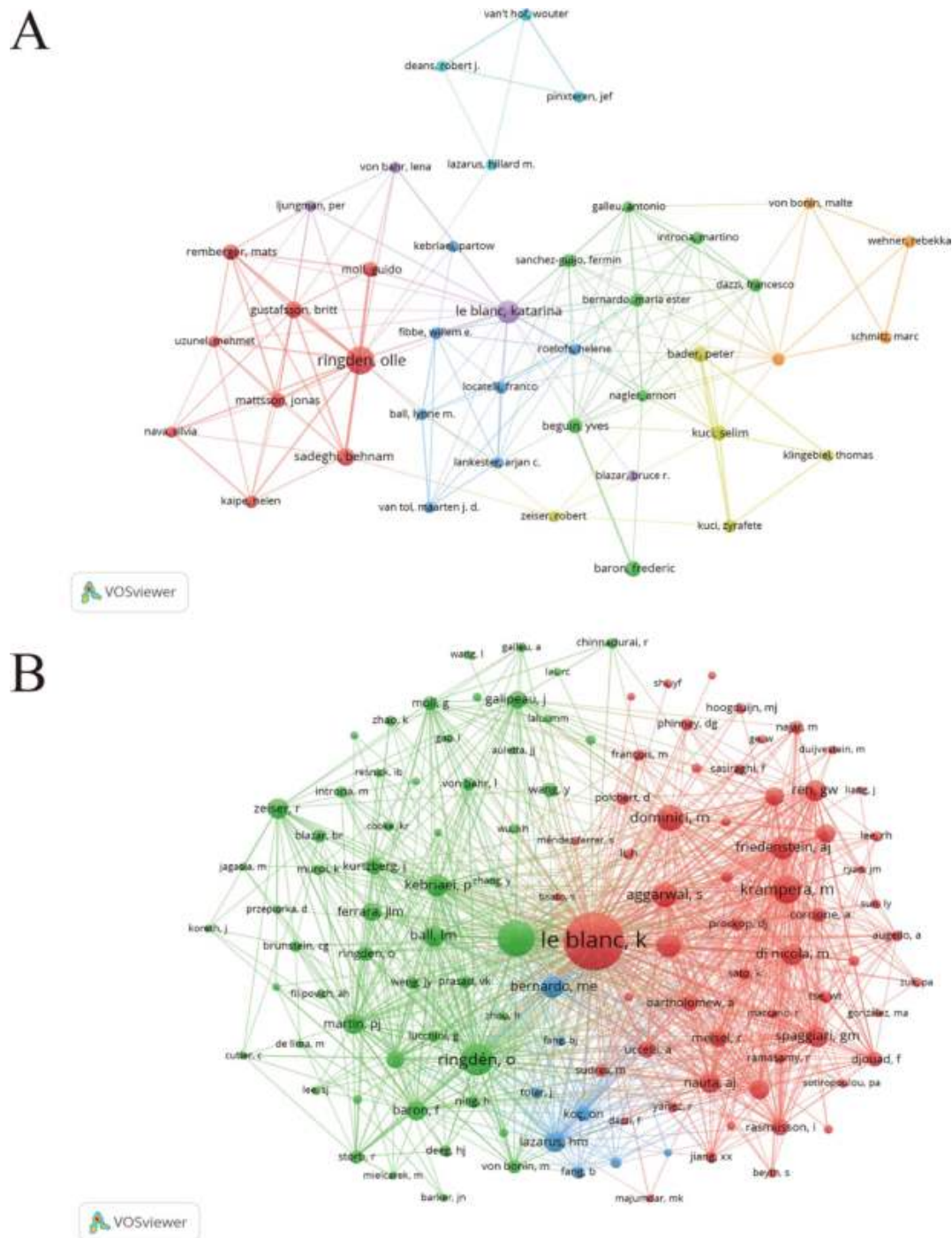


Fig. 7 The visualization of authors (A) and co-cited Authors (B) on research of MSC in GVHD

immunity significantly influences MSC immunomodulatory functions, proliferation, differentiation, self-renewal, and tissue repair [34]. In 2004, Le Blanc K reported a landmark case in *Lancet*, where MSC transplantation in a patient with severe, treatment-refractory grade IV GVHD resulted in successful survival, thereby establishing a basis for future research [35]. In 2006, he further highlighted the therapeutic potential of MSCs in treating

GVHD and autoimmune inflammatory bowel disease [36], and a 2008 multicenter Phase II trial in Lancet confirmed that the infusion of ex vivo expanded MSCs following HCT may effectively treat steroid-resistant acute GVHD [37]. Overall, these studies predominantly focus on the mechanisms and therapeutic efficacy of MSC-based treatments for GVHD.

Table 4 Top 10 co-cited references on research of MSCs in GVHD

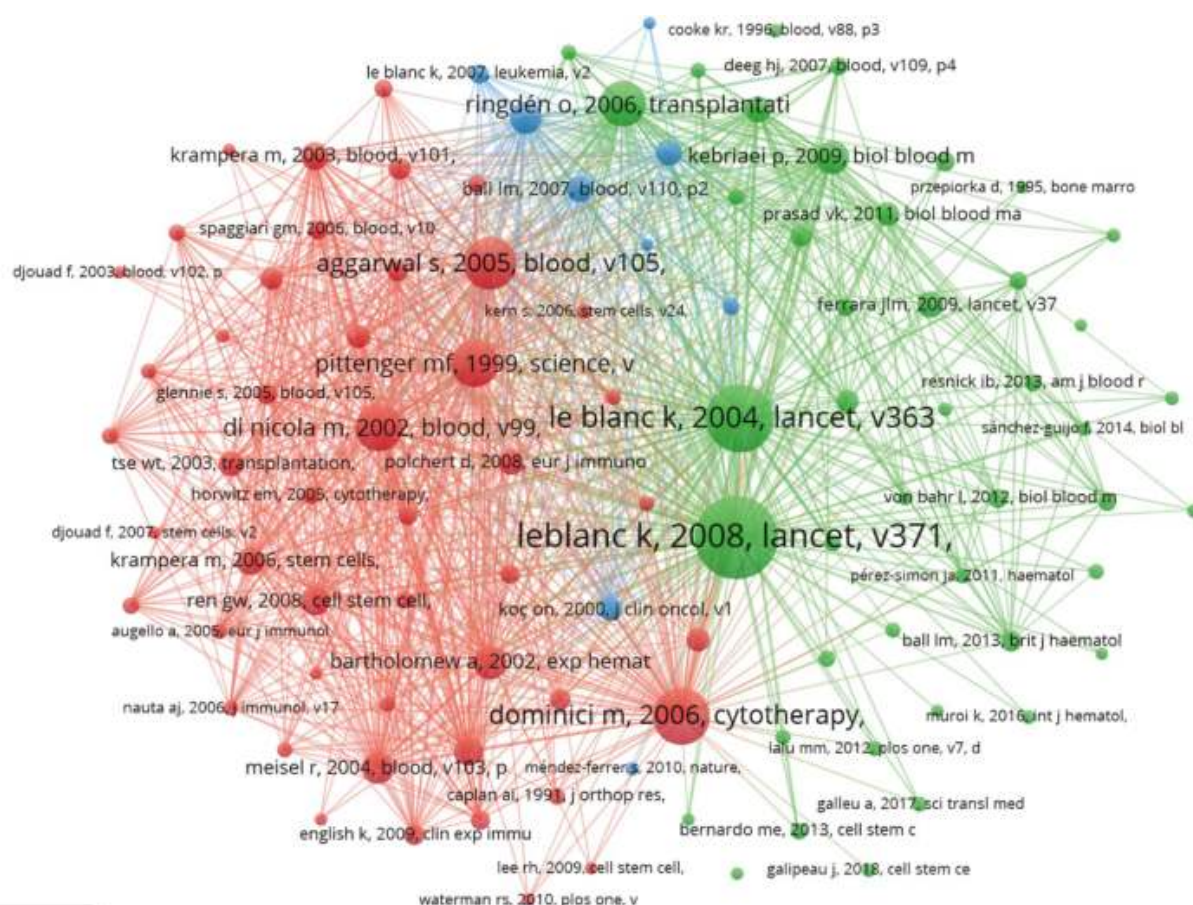
Rank	Co-cited reference	Citations
1	leblanc k, 2008, lancet, v371, p1579	390
2	le blanc k, 2004, lancet, v363, p1439	308
3	dominici m, 2006, cytotherapy, v8, p315	247
4	aggarwal s, 2005, blood, v105, p1815	226
5	pittenger mf, 1999, science, v284, p143	199
6	di nicola m, 2002, blood, v99, p3838	194
7	ringdén o, 2006, transplantation, v81, p1390	188
8	bartholomew a, 2002, exp hematol, v30, p42	130
9	kebriaei p, 2009, biol blood marrow tr, v15, p804	128
10	meisel r, 2004, blood, v103, p4619	122

In terms of co-cited authors, Le Blanc K is the most frequently cited, followed by Olle Ringdén. The substantial citation frequency of these two researchers underscores their pivotal contributions in establishing both the theoretical framework and experimental evidence for MSC-based therapies in GVHD.

Knowledge base

Co-cited references—those cited together by multiple publications—form the foundation of research in a given field. In this bibliometric study, we selected the top 10 most frequently co-cited references. Two of Le Blanc K's most cited articles, published in *Lancet*, have already been discussed in the previous section and will not be repeated here. Dominici et al. (2006) established the minimum criteria for defining multipotent mesenchymal stromal cells (MSCs): MSCs must adhere to plastic under standard culture conditions, express surface markers CD105, CD73, and CD90, lack expression of CD45, CD34, CD14 or CD11b, CD79 α or CD19, and HLA-DR, and must be capable of differentiating into osteoblasts, adipocytes, and chondroblasts in vitro [38]. But now we have realized that MSCs can be isolated from various tissues, including muscle, umbilical cord, liver, placenta, skin, amniotic fluid, synovial membrane, and tooth root [39].

There is no consistency in the use of cell surface antigens for the isolation of MSCs and there is no marker

**Fig. 8** The visualization of co-cited references on research of MSC in GVHD

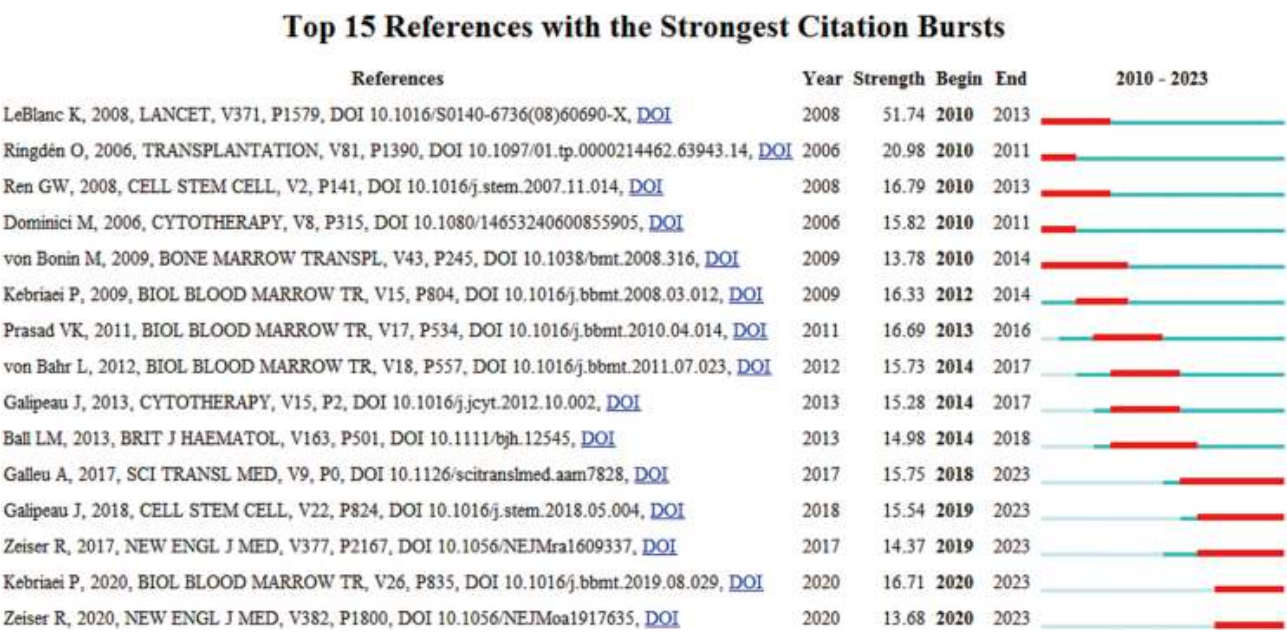


Fig. 9 Top 13 references with strong citation bursts. A red bar indicates high citations in that year

that uniquely identifies MSCs that could be used reliably for their isolation. MSC populations have natural variation in the expression of cell surface markers, because MSCs are dynamic and exhibit phenotypic variation over time “plasticity” [40].

Aggarwal et al. (2005) reported in Blood that MSCs modulate the cytokine secretion profiles of dendritic cells (DCs), naïve and effector T cells, and natural killer (NK) cells, thereby inducing an anti-inflammatory or tolerant phenotype [41]. In 1999, Pittenger et al. proposed that MSCs are multipotent cells that can differentiate into a variety of mesenchymal tissues—including bone, cartilage, fat, tendon, muscle, and bone marrow stroma—thus offering new therapeutic avenues for tissue repair [42]. Di Nicola et al. (2002) demonstrated that bone marrow MSCs strongly inhibit T lymphocyte proliferation, likely through the secretion of soluble factors rather than by inducing apoptosis [43]. Olle Ringdén et al. (2006) further concluded that bone marrow MSCs are a promising treatment for steroid-resistant acute GVHD [21]. Bartholomew et al. (2002) observed that MSCs can inhibit lymphocyte proliferation in vitro, thereby extending skin graft survival [44]. Kebriaei et al. (2009) also suggested that MSCs represent a novel therapeutic option for GVHD [45]. Moreover, Meisel et al. (2004) discovered that the indoleamine 2,3-dioxygenase (IDO)-mediated metabolism of tryptophan in MSCs is a novel mechanism for T-cell suppression, providing new research insights [46]. Collectively, these top 10 co-cited references primarily focus on the biological functions of MSCs, their identification, and their therapeutic mechanisms in

treating GVHD, thereby forming the essential knowledge base for subsequent research in this area.

Hotspots and frontiers

Recent research has increasingly focused on references that experience citation bursts, as these indicate emerging themes within the field [47]. Analysis of the most highly cited references (see Table 5) reveals that current research primarily addresses the biological roles and pathogenesis of MSCs in GVHD, as well as their potential therapeutic applications. In addition to burst references, keyword analysis has proven to be an effective tool for identifying research hotspots. Table 6 highlights key terms such as “extracellular vesicles,” “exosomes,” “cytokines,” and “immunotherapy.” Based on clustering and trend analyses of keywords (Fig. 10), it is evident that recent research on MSCs in GVHD is predominantly focused on extracellular vesicles and exosomes.

Extracellular vesicles and exosomes

Extracellular vesicles (EVs) are a collective term for secreted vesicles—including exosomes, microvesicles, and apoptotic bodies—that serve as membrane-bound carriers of proteins, lipids, carbohydrates, and nucleic acids. When loaded with mRNA or miRNA, these vesicles can modulate protein translation and gene expression [48, 49]. Exosomes, typically 30–150 nm in size, are formed by the fusion of multivesicular bodies with the plasma membrane and are characterized by marker proteins such as CD63, CD9, CD81, Syntenin-1, and TSG101 [50, 51]. Due to their small size and fluid structure, exosomes can traverse physiological barriers, and they have

Table 5 The main research contents of the 11 references with strong citations bursts

Rank	Strength	Main research content
1	51.74	Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study
2	20.98	Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease
3	16.79	Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide
4	15.82	Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement
5	13.78	Treatment of refractory acute GVHD with third-party MSC expanded in platelet lysate-containing medium
6	16.33	Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease
7	16.69	Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal™) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study
8	15.73	Long-term complications, immunologic effects, and role of passage for outcome in mesenchymal stromal cell therapy
9	15.28	The mesenchymal stromal cells dilemma—does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road?
10	14.98	Multiple infusions of mesenchymal stromal cells induce sustained remission in children with steroid-refractory, grade III-IV acute graft-versus-host disease
11	15.75	Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation

demonstrated significant therapeutic potential in diseases including Alzheimer’s, spinal cord injury, stroke, various autoimmune conditions, GVHD, rheumatoid arthritis, autoimmune hepatitis, colitis, diabetes, and systemic sclerosis [52–55]. EV secretion is now recognized as a principal mechanism for intercellular molecular exchange and signal transduction [56]. Recent studies suggest that because MSCs tend to accumulate in the lungs and spleen and are rapidly cleared from circulation, their paracrine effects—mediated largely through EVs—are crucial for therapeutic efficacy [57, 58]. MSC-derived EVs play a key role in immunomodulation, anti-inflammation, and tissue regeneration. In vitro data consistently show that these EVs inhibit CD3⁺ T cell activation and induce apoptosis in both CD3⁺ and CD4⁺ T cells [59–61]. Clinical case reports further indicate that MSC-derived EVs can reduce levels of IL-1 β , TNF- α , and IFN- γ , thereby improving survival and mitigating tissue damage

Table 6 Top 20 keywords on research of MSCs in GVHD

Rank	Keywords	Counts	Rank	Keywords	Counts
1	mesenchymal stem cells	164	11	allogeneic hematopoietic stem cell transplantation	21
2	graft-versus-host disease	122	12	exosomes	19
3	hematopoietic stem cell transplantation	68	13	regulatory t cells	19
4	immunomodulation	64	14	regenerative medicine	18
5	cell therapy	54	15	umbilical cord	17
6	immunosuppression	47	16	hematopoietic stem cells	16
7	extracellular vesicles	25	17	immuno-therapy	16
8	transplantation	23	18	allogeneic stem cell transplantation	16
9	bone marrow	21	19	cytokines	15
10	bone marrow transplantation	21	20	stem cell transplantation	15

in GVHD patients [62]. Additionally, high expression of specific miRNAs—such as miR-223—in MSC EVs has been linked to reduced T cell migration to target organs [63]. Emerging evidence also supports the use of EV levels as early biomarkers for acute GVHD [64–66]. Beyond acute GVHD, EVs from placenta-derived MSCs have shown promise in modulating skin inflammation and fibrosis in chronic GVHD [67, 68]. Mechanistically, MSC EVs may exert their therapeutic effects by rebalancing immune dysregulation, reducing oxidative stress, and suppressing pathological fibrosis [69]. Recent innovations include the development of human umbilical cord MSC-derived EVs loaded with arsenic trioxide (huc-ev-ato), which alleviate GVHD severity by inhibiting mTOR activity and repolarizing M1 to M2 macrophages [70]. While the PD-1/PD-L1 pathway can enhance the therapeutic impact of MSC EVs [71], overexpression of PD-L1 on EVs early after transplantation has been associated with the onset of GVHD [72]. Moreover, NK cell-derived EVs, rich in cytolytic proteins such as perforin, granzymes, granulysin, and Fas ligand, have demonstrated potential graft-versus-leukemia (GVL) effects [73, 74]. Overall, while significant progress has been made in harnessing MSC-derived EVs for GVHD treatment, challenges remain in optimizing their isolation, dosing, delivery schedule, and long-term safety.

Summary

Mesenchymal stromal cells (MSCs) have emerged as a pivotal therapeutic tool in the management of graft-versus-host disease (GVHD), as evidenced by the rapidly increasing number of publications and global research

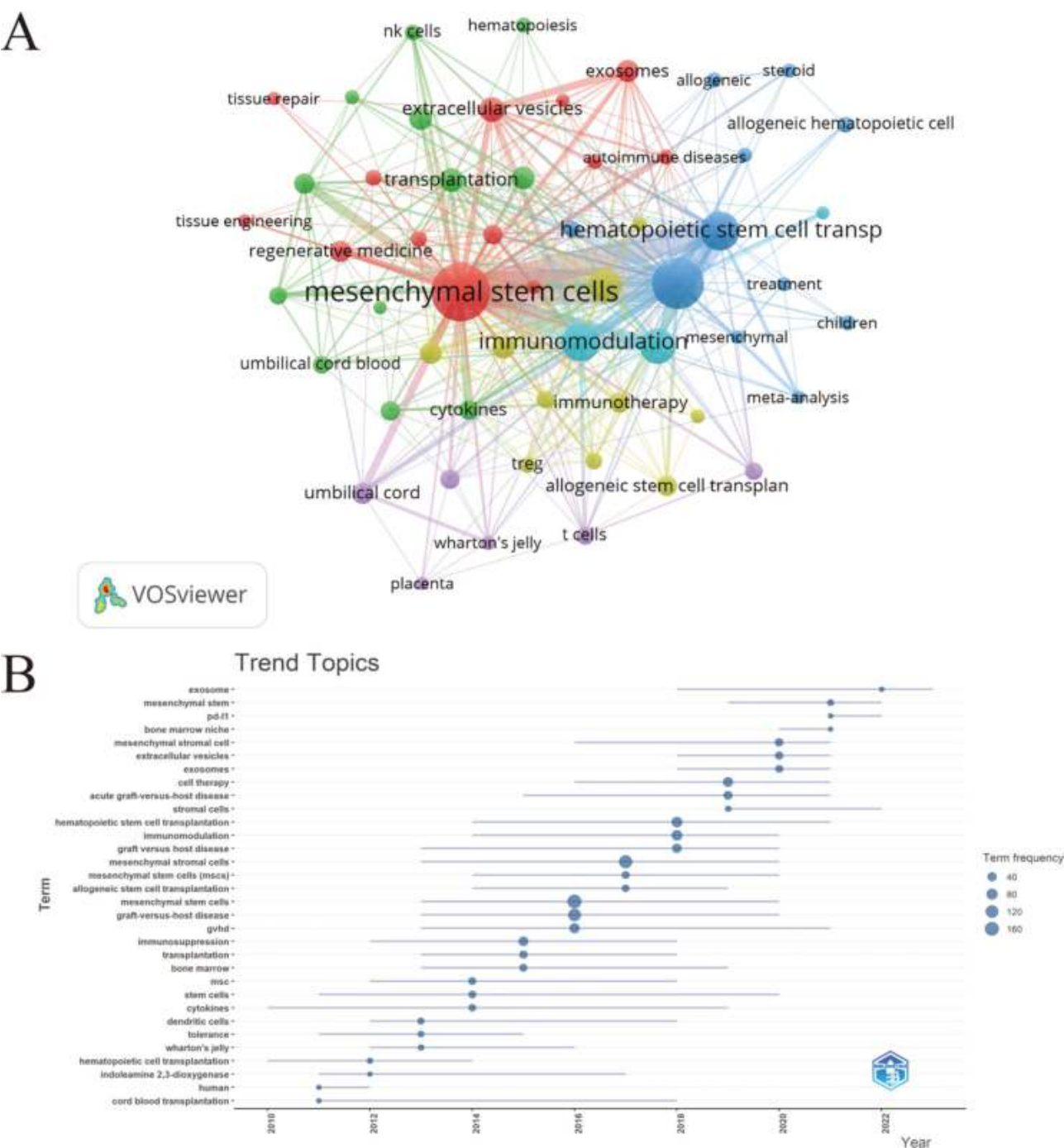


Fig. 10 Keyword cluster analysis (A) and trend topic analysis (B)

efforts, particularly in China and the United States. While traditional MSC therapies focus on cell-based approaches, recent studies highlight the substantial potential of MSC-derived extracellular vesicles (EVs) and exosomes as acellular alternatives. These vesicles not only mediate critical immunomodulatory and regenerative functions but also overcome some limitations of direct cell therapy, such as poor tissue homing and rapid

clearance. Despite promising preclinical and early clinical results, further research is essential to optimize EV isolation, dosing, delivery methods, and long-term safety. Strengthened international collaboration and focused translational studies will be key to advancing EV-based therapies, which may ultimately revolutionize the clinical management of GVHD.

Abbreviations

GVHD	Graft-versus-host Disease
MSCs	Mesenchymal stromal Cells
HCT	Hematopoietic Cell Transplantation
WoS	Web of Science
NK	Natural Killer
EVs	Extracellular Vesicles
GVL	Graft-versus-leukemia

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