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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, 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 *WJD* as 4.2; JIF without journal self cites: 4.1; 5-year JIF: 4.2; JIF Rank: 40/186 in endocrinology and metabolism; JIF Quartile: Q1; and 5-year JIF Quartile: Q2.

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SCIENTOMETRICS

Role of macrophage polarization in diabetic foot ulcer healing: A bibliometric study

You-Wen Zhang, Lei Sun, Yan-Nan Wang, Shi-Yu Zhan

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Abstract

BACKGROUND

Diabetic foot ulcers (DFUs) are a significant contributor to disability and mortality in diabetic patients. Macrophage polarization and functional regulation are promising areas of research and show therapeutic potential in the field of DFU healing. However, the complex mechanism, the difficulty in clinical translation, and the large heterogeneity present significant challenges. Hence, this study was to comprehensively analyze the publication status and trends of studies on macrophage polarization and DFU healing.

AIM

To examine the relevant literature on macrophage polarization in DFU healing.

METHODS

A bibliometric analysis was conducted using the Web of Science database. Relevant literature was retrieved from the Web of Science Core Collection database between 2013 to 2023 using literature visualization and analysis software (VOSviewer and CiteSpace) and bibliometric online platforms. The obtained literature was then subjected to visualization and analysis of different countries/regions, institutions, journals, authors, and keywords to reveal the research's major trends and focus.

RESULTS

The number of publications on the role of macrophage polarization in DFU healing increased rapidly from 2013 to 2023, especially in the latter period.

Chinese researchers were the most prolific in this field, with 217 publications, while American researchers had been engaged in this field for a longer period. Qian Tan of Nanjing Drum Tower Hospital and Qian Ding of Nanjing University were the first to publish in this field. Shanghai Jiao Tong University was the institution with the most publications (27). The keywords "bone marrow", "adjustment, replacement, response, tissue repair", and "activation, repair, differentiation" appeared more frequently. The study of macrophage polarization in DFU healing focused on the regulatory mechanism, gene expression, and other aspects.

CONCLUSION

This study through the bibliometric method reveals the research trends and development trends in this field of macrophage polarization in DFU healing from 2013 to 2023 in the Web of Science Core Collection database. The key hotspots in this field mainly include the regulation of macrophage activation, gene expression, wound tissue repair, and new wound materials. This study provides references for future research directions.

Key Words: Diabetic foot; Wound healing; Macrophage polarization; Bibliometric analysis; Research cooperation; Research trend

Core Tip: This study was to comprehensively analyze the publication status and trends of studies on macrophage polarization and diabetic foot ulcer (DFU) healing. The number of publications on the role of macrophage polarization in DFU healing increased rapidly from 2013 to 2023, Chinese researchers were the most prolific in this field, while American researchers had been engaged in this field for a longer period. The keywords "bone marrow", "adjustment, replacement, response, tissue repair", and "activation, repair, differentiation" appeared more frequently. The study of macrophage polarization in DFU healing focused on the regulatory mechanism, gene expression, and other aspects.

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INTRODUCTION

The latest data released by the International Diabetes Federation in 2019 indicated approximately 463 million diabetics worldwide, with an estimated increase to 700 million by 2045[1]. The increasing number of diabetics will inevitably increase the number of patients with diabetic foot, which is one of the most common chronic complications of diabetes, and a leading cause of nontraumatic amputation and disability and death in diabetics[2,3]. Furthermore, the high recurrence rate of diabetic foot has also imposed a huge economic burden, so it is imperative to understand the trend of diabetic foot. Macrophages are a type of white blood cells in tissues, originating from monocytes, and play a crucial role in nonspecific defense (innate immunity) and specific defense (cellular immunity) *in vivo*. Their primary functions include the phagocytosis of cell fragments and pathogens in a fixed or free state, as well as the activation of lymphocytes or other immune cells to respond to pathogens. Macrophage polarization refers to the process of mature macrophages developing different functional phenotypes under the stimulation of a special microenvironment. According to the different activation states and functions, macrophages can be categorized into classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages are usually activated by bacterial, viral, and other pathogen components [such as lipopolysaccharide (LPS)] or cytokines (such as interferon-gamma), leading to the secretion of proinflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-6, and IL-12. M1 macrophages are characterized by strong antibacterial and anti-tumor abilities, promoting helper T (Th)-1 type cells immune responses and contributing to cellular immunity. M2 macrophages are usually activated by anti-inflammatory cytokines (*e.g.*, IL-4, IL-13) or immune complexes, producing anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF-β). M2 macrophages play a crucial role in tissue repair, angiogenesis promotion, and inflammation suppression, with significant associations with Th2-type immune responses and humoral immunity. Macrophage polarization is essential for pathogen defense, inflammation, tissue repair, and homeostasis.

Macrophage polarization is an emerging area of research. Increasing studies are focusing on how macrophage polarization affects healing, especially in dysregulated wound healing, such as diabetic wound healing[4,5]. Macrophages play critical regulatory roles at all stages of tissue repair and fibrosis[4,5]. In response to injury, different types of macrophages exhibit a range of functions at different stages of injury in different organ systems, including pro-inflammatory, anti-inflammatory, pro-fibrotic, pro-wound healing, pro-absorptive, and tissue regenerative roles[6,7]. Macrophage polarization exerts an important role in diseases involving tissue repair, such as chronic wounds[8], myocardial infarctions[9], periodontitis[10], inflammatory bowel disease[11], and liver disease[12]. Therefore, macrophage polarization and functional regulation are a promising area of research and show therapeutic potential in the field of diabetic

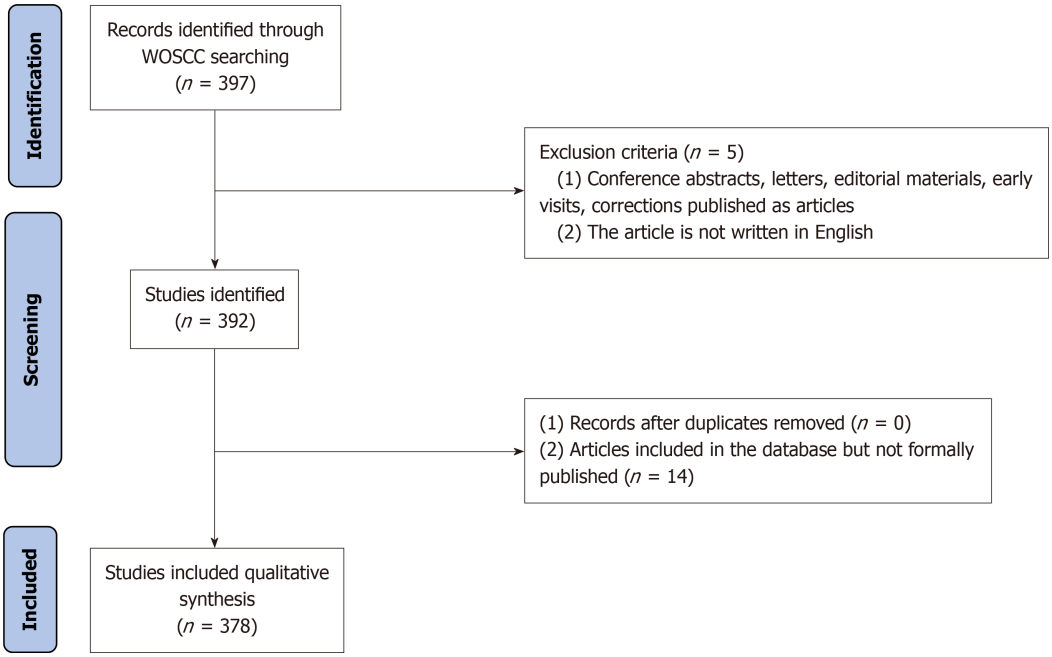


Figure 1 Flowchart of literature retrieval and screening results. WOSCC: Web of Science Core Collection.

foot ulcer (DFU) healing. However, the complex mechanism, the difficulty in clinical translation, and the large heterogeneity present significant challenges.

Bibliometric analysis is an interdisciplinary method for quantitative analysis of related literature in a specific research field. Based on published literature, this statistical analysis tool is utilized to establish links between published literature and highlight research hotspots in certain academic fields, thereby quantitatively investigating the trends in a research topic[13]. Compared with traditional reviews, bibliometric analysis has shown greater advantages in objectively presenting the internal conceptual structure and potential associations of a large number of publications. Therefore, based on the bibliometric method, this paper includes the literature related to macrophage polarization in the healing of DFUs, analyzes the countries, institutions, journals, references, research hotspots, and key research areas, ascertains the status and trends in this research area, and identifies research hotspots and future research directions.

MATERIALS AND METHODS

Data sources and search strategy

The bibliometric analysis is widely used in the Web of Science Core Collection (WOSCC) database, which provides comprehensive statistical analysis of multidisciplinary information[14]. In this study, the WOSCC database was comprehensively searched for literature on the role of macrophage polarization in DFUs between 2013 and 2023 (up to 31 December 2023) using MeSH terms. The specific search strategies used were as follows: (1) TS = (macrophage polarization); (2) TS = (diabetic foot) OR TS = (diabetic feet) OR TS = (diabetes foot) OR TS = (DFU) OR TS = (diabetic foot gangrene) OR TS = (lower extremity peripheral arterial disease) OR TS = (diabetic peripheral neuropathy) OR TS = (diabetes complications) OR TS = (diabetic wound) OR TS = (diabetic ulcer) OR TS = (foot, diabetic) OR TS = (feet, diabetic) OR TS = (foot ulcer, diabetic) OR TS = (diabetic foot) OR TS = (DFU); and (3) Including "TS = (macrophage polarization)" and "TS = (diabetic foot) OR TS = (diabetic feet) OR TS = (diabetes foot) OR TS = (DFU) OR TS = (diabetic foot gangrene) OR TS = (lower extremity peripheral arterial disease) OR TS = (diabetic peripheral neuropathy) OR TS = (diabetes complications) OR TS = (diabetic wound) OR TS = (diabetic ulcer) OR TS = (foot, diabetic) OR TS = (feet, diabetic) OR TS = (foot ulcer, diabetic) OR TS = (diabetic foot) OR TS = (DFU)". Literature was further excluded based on exclusion criteria on language and article type: (1) Conference abstracts, letters, editorial material, early access, corrections published as articles; and (2) Articles not written in English. Literature retrieval was conducted independently by two researchers and the results are presented in Figure 1.

Statistical analysis

Citespace (Version 6.3.R1), VOSviewer (Version 1.6.20), and an online platform (https://bibliometric.com/) were adopted for data analysis and result visualization. CiteSpace is a Java-based visualization tool that offers a variety of visualization options, including network maps, centrality metrics, and burst detection algorithms, which illustrate clusters and dynamics related to a specific scientific topic[15]. The centrality of nodes is calculated to reveal their importance in the network[16]. Burst maps detect keywords and references, which can identify a sudden and significant increase in scientific activity during a certain period[17]. VOSviewer is another Java-based bibliometric analysis software

Table 1 The 10 countries/regions with the highest number of publications in the field

Rank	Country/region	Number of articles	Citations	Average article citations	H-index	Centrality
1	China	217	4485	20.67	33	0.57
2	United States	72	2869	39.85	30	0.55
3	Germany	20	1134	56.7	13	0.29
4	Italy	12	316	26.33	7	0.08
5	Japan	12	612	51	9	0.07
6	Australia	11	178	16.18	8	0.19
7	England	10	369	36.9	9	0.08
8	India	9	144	16	5	0
9	Iran	8	203	25.38	5	0.02
10	Russia	7	343	49	3	0.02

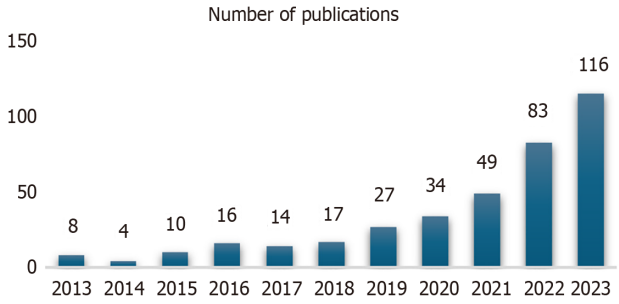


Figure 2 Publications on macrophage polarization in diabetic foot ulcer from 2013 to 2023.

that allows the exploration and visualization of research features from different perspectives[18]. In network visualization maps, each node corresponds to parameters such as country/region, institution, journal, author, or keyword. The node size represents its strength (*e.g.*, number of publications, citations, and frequency), while the thickness of the links represents the strength of network association[19]. The online bibliometric analysis platform was used to visualize the country/region distribution and international collaborations. The diverse analytical tools employed in this study enabled comprehensive and detailed data analyses and provided valuable insights into the current status, knowledge base, research trends, and emerging themes in the role of macrophage polarization in DFU healing.

RESULTS

General characteristics of publications

Papers published between 2013 and 2023 are statistically analyzed (Figure 1). A total of 397 papers were retrieved. After excluding five papers, including conference abstracts, letters, editorial materials, early access, and corrections, 392 papers were included in the analysis. After importing the data into CiteSpace, no literature was screened for formatting errors or duplicates. Additionally, 14 papers that were included in the database but not officially published were deleted. Finally, 378 papers were enrolled. Between 2013 and 2023, the number of publications steadily increased in each year, except for 2014 and 2017, when the number of publications decreased. The peak was reached in 2023 (Figure 2). Among the 378 publications, 81.75% were published in the last five years. The total number of citations was 10352, with an average of 27.39 citations per paper. The H-index was 56.

Analysis of national/regional article output and collaboration

The included literature originated from 47 countries or regions. Researchers from China had the most publications (217 articles, 57.41% of the total), followed by the United States (72 articles, 19.05% of the total) and Germany (20 articles, 5.29% of the total) (Figure 3A and B). Figure 3C depicts 74 links and 47 nodes, with a density of 0.0675, which demonstrates a collaborative network between countries/regions. Among the ten countries/regions with the largest number of articles, China (0.57) had the highest centrality, followed by the United States (0.55) and Germany (0.29) (Table 1). Figure 3D and E demonstrates an evident trend of global collaboration. Among the top 10 countries/regions in the number of publications, China, the United States, and European countries most frequently cooperated with other countries/regions.

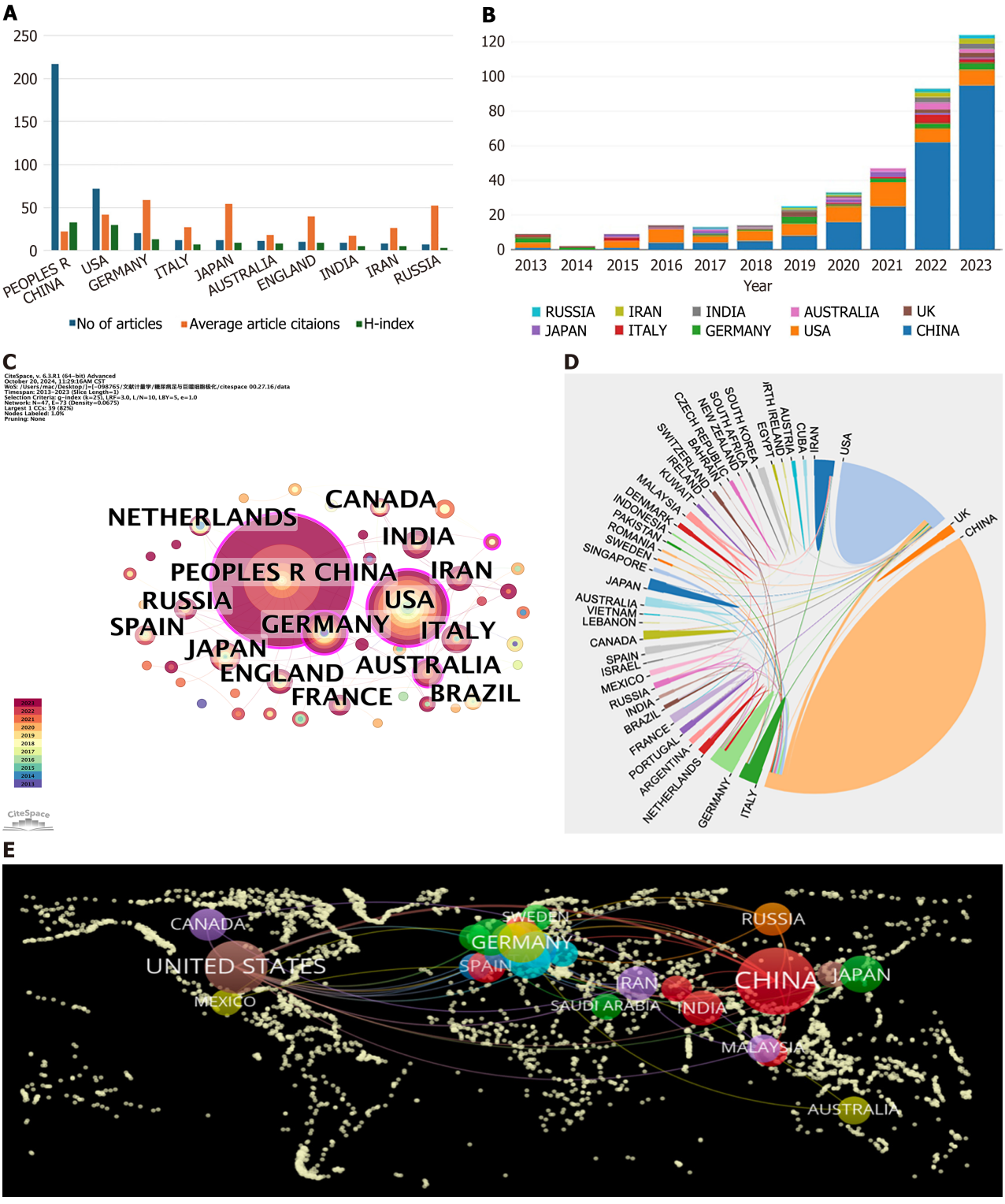


Figure 3 Analysis of national/regional article output and collaboration. A: Total number of publications, average citation frequency, and H-index for the 10 most productive countries/regions; B: Number of publications per year for the 10 most productive countries/regions; C: Collaborative networks between countries/regions; D: Inter-country collaborative research; E: Inter-country collaborations plotted on a world map.

Institutional analysis

The data analysis revealed that 250 institutions contributed to the field. CiteSpace generated a graphical visualization of the institutional collaboration network (Figure 4). Institutions with ≥ 10 publications (Table 2) included Shanghai Jiao Tong University, Chinese Academy of Sciences, Sichuan University, Harvard University, and Harvard Medical School. Among the nine institutions with at least 10 publications, Shanghai Jiao Tong University exhibited the highest centrality (0.18), followed by the Chinese Academy of Sciences (0.13) and Harvard University (0.13).

Table 2 Institutions with ≥ 10 publications in the field

Rank	Institution	Number of articles	Citations	Average article citations	H-index	Centrality
1	Shanghai Jiao Tong University	27	737	27.30	15	0.18
2	Chinese Academy of Sciences	17	548	32.24	10	0.13
3	Sichuan University	15	93	6.2	7	0.02
4	Harvard University	13	312	24	9	0.13
5	Harvard Medical School	10	292	27.2	7	0.04
6	Sun Yat-sen University	10	97	9.7	5	0.07
7	Nanjing University	10	160	16.00	6	0.01
8	Shanghai University of Traditional Chinese Medicine	10	63	6.3	4	0.02

Figure 4 Collaborative networks between institutions.

Analysis of authors and co-cited authors

Based on the data analysis, Figure 5A depicts the collaborative network among authors, with 398 authors contributing to this field. Among them, Qian Tan from Nanjing Drum Tower Hospital and Xiao-Feng Ding from Nanjing University had the most publications, both of which were 7 papers. The threshold of the publications of core authors is expressed as the formula, $N = 0.749\sqrt{(n\_max)}$, where n_max is the number of papers issued by the most prolific authors. After calculation, it was determined that the authors with ≥ 3 publications were defined as prolific authors. There were 22 prolific authors, with 92 articles, accounting for 24.34%. Among them, 8 authors had ≥ 5 publications (Table 3), with 47 articles, accounting for 12.43%, suggesting that despite the high overall number of publications by core authors, a core group of authors in the research field has not yet been formed. By analyzing the authors' co-citation network, authors with ≥ 20 citations were defined as key researchers (Figure 5B and C). The size of each circle represented the number of publications of an author, with more publications generating a larger circle[20]. "Total link strength" refers to the cumulative strength of all links between two nodes in the network graph. Links between nodes represent cooperative relationships, co-occurrence relationships, and reference relationships, and each link has a weight or strength value. The total link strength is the sum of the strength of all links connecting two nodes. It was found that Mantovani A (69) had the highest co-citation frequency and the highest tertiary lymphoid structures, followed by Gordon S (68) and Falanga V (62) (Supplementary Table 1).

Analysis of journals and co-cited journals

Between 2013 and 2023, a total of 378 research articles related to macrophages and DFUs were published in 215 journals (Table 4). According to the statistical analysis of impact factor in 2023, there were 71 journals with ≥ 2 articles, and an

Table 3 Authors with ≥ 5 publications in the field

Rank	Author	Number of articles	Citations	Average article citations	H-index
1	Qian Tan	7	38	5.43	4
2	Xiao-Feng Ding	7	32	4.6	3
3	KA Gallagher	6	723	103.3	6
4	Peng Wang	6	73	12.17	3
5	Shi-Yan Li	6	32	6	3
6	Kimberly AM	5	206	41.2	5
7	Ping Yang	5	20	4	3
8	Wei Li	5	15	3	3

Table 4 Top 10 journals with the most publications in the field

Rank	Journal	Number of articles	Citations	Average article citations	H-index
1	*Advanced Functional Materials*	12	481	40.08	8
2	*International Journal of Molecular Sciences*	11	186	16.91	7
3	*Advanced Healthcare Materials*	9	49	5.44	3
4	*Advanced Science*	8	154	19.25	5
5	*Frontiers in Immunology*	8	83	10.38	4
6	*Diabetes*	7	395	56.43	6
7	*International Journal of Biological Macromolecules*	7	53	7.57	4
8	*Journal of Investigative Dermatology*	6	250	41.67	6
9	*Biomaterials*	6	239	39.83	6
10	*Chemical Engineering Journal*	6	148	24.67	4

average impact factor of 7.82, indicating high academic levels and strong influences of journals in this field. Among the top 10 journals that published articles on macrophage polarization in DFU healing, only 4 journals had an impact factor ≥ 10, and the number of articles published in these journals accounted for 9.26% of the total included literature, indicating a challenge for research articles in this field to be published in high-quality journals. The 10 journals with the most publications listed in the co-cited journals in this field are shown in Supplementary Table 2. Most papers were published in *Advanced Functional Materials* (12), followed by *International Journal of Molecular Sciences* (11) and *Advanced Healthcare Materials* (9). VOSviewer generated a network visualization of the journals' co-citation analysis (Figure 6). Only journals with at least 20 citations are listed. Of the 259 journals that met the criteria, the top 3 most frequently cited journals were *Diabetes*, *Biomaterials*, and *Journal of Immunology*. Dual-map overlay of journals (ellipse vertical axis represents the volume of papers and the horizontal axis represents the number of authors) represents the link from the field of the citing journal to the field of the cited journal. Journal dual-map overlay provides the citing and cited matrix of the journal. Using the *Z* scores feature of Citespace software, the results showed the dual maps between the journals that published literature and the cited journals within 2013-2023. The colored paths in Figure 7 represent the citation relationships in highly active research areas. The published papers mainly focus on medical and clinical journals, molecular, biology, and immunology, while cited papers are mainly in the molecular, biology, immunology, and medical journals. The results indicate that this field is a multidisciplinary and cross-cutting area and has received attention from multidisciplinary experts, providing a theoretical and technical basis for the study of macrophage polarization in DFUs, and suggesting the importance and necessity of interdisciplinary cooperation in the future.

Commonly cited literature analysis

The co-cited literature analysis demonstrates the relationship between the literature. Considering the number of references cited, the minimum number of literature citations was set as 15, and a total of 71 documents were retrieved for analysis. The 10 most frequently co-cited documents are listed in Supplementary Table 3. The most frequently co-cited article was "Macrophage polarization and diabetic wound healing" by Louiselle *et al*[21] in 2021, published in the journal *Translational Research*. The next most frequently cited article was "Wound healing and its impairment in the diabetic foot" by Falanga[22] in 2005, published in the *Lancet*. The third most frequently cited article was "Macrophage-Mediated Inflammation in Normal and Diabetic Wound Healing" by Boniakowski *et al*[23] in 2017, published in the *Journal of Immunology* (Figure 8).

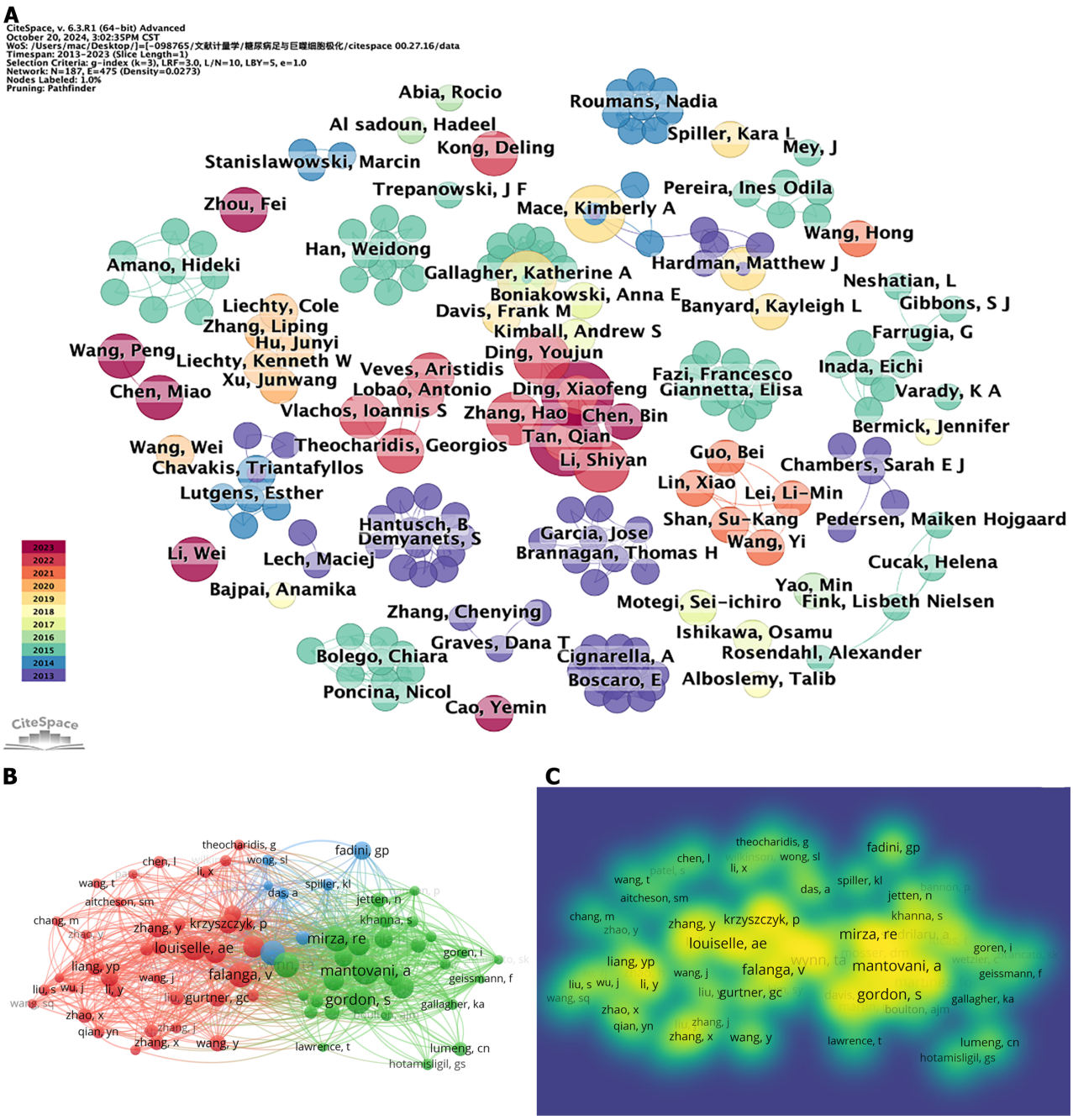


Figure 5 Collaborative network among authors. A: A visualization map of author collaboration; B: A visualization map of authors with ≥ 20 citations; C: Network map showing author co-citation frequency.

Keyword co-occurrence, aggregation, and emergence analysis

Keywords highly condense the content of the article, and a high frequency of co-occurrence of a keyword in a field suggests that it may be a research hotspot in the field. The keywords were used as nodes to visualize and analyze the literature, and 330 keywords were obtained from the data analysis (Figure 9A). The time-zone map of keywords (Figure 9B) revealed that from 2013 to 2023, in the study of macrophage polarization in DFU healing, keywords such as "protein", "migration", and "prevention" emerged as new research hotspots over time. The keywords with a minimum of two occurrences were co-visualized through VOSviewer (Figures 9C and D). Table 5 presents the ten most frequent keywords. Macrophage polarization had the highest frequency (123), followed by inflammation (85), activation (68), wound healing (65), polarization (63), and expression (61). Keywords with high centrality indicate the area of significant interest within the field, with centrality ranging from 0 to 1. The top 10 keywords in terms of centrality were bone marrow, angiogenesis, insulin resistance, alternative activation, complications, adipose tissue, chronic wound healing, risk, chitosan, and dendritic cells.

The keywords were numbered and clustered by Citespace (Figure 10A) and were divided into 14 major categories (Table 5). The study's Q = 0.7231 and S = 0.8678 indicated that this data analysis was reasonable. The results were shown as "0 diabetic wounds", "1 mesenchymal stem cell", "2 reactive oxygen species", "3 multifunctional hydrogels", "4 neutrophil extracellular traps", "5 diabetic retinopathy", "6 endothelial cells", "7 adipose tissue", "8 inflammasome", "9

Table 5 Frequency and centrality of the top 10 key words

	Rank	Frequency	Centrality	Year	Key word
Ranked by frequency	1	123	0.06	2014	Macrophage polarization
	2	85	0.07	2013	Inflammation
	3	68	0.05	2013	Activation
	4	65	0.02	2016	Wound healing
	5	63	0.08	2015	Polarization
	6	61	0.1	2013	Expression
	7	43	0.05	2018	Repair
	8	42	0.07	2013	Cells
	9	41	0.21	2013	Angiogenesis
	10	39	0.1	2013	Macrophages
Ranked by centrality	1	14	0.33	2013	Bone marrow
	2	41	0.21	2013	Angiogenesis
	3	32	0.20	2013	Insulin resistance
	4	18	0.19	2013	Alternative activation
	5	12	0.19	2016	Complications
	6	16	0.15	2013	Adipose tissue
	7	3	0.14	2018	Chronic wound healing
	8	6	0.13	2019	Risk
	9	5	0.11	2015	Chitosan
	10	5	0.11	2013	Dendritic cells

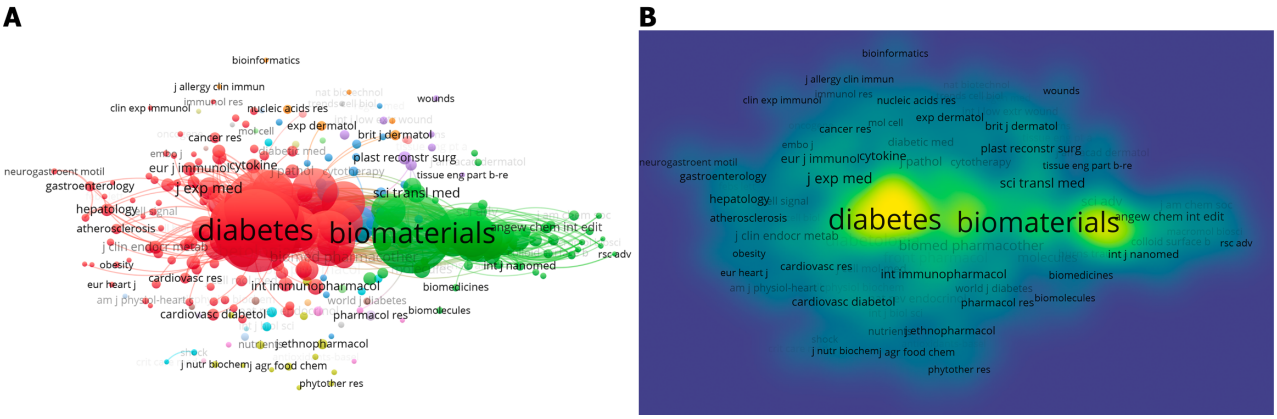


Figure 6 VOSviewer generated a network visualization of the journals' co-citation analysis. A: VOSviewer-generated network visualization map of journal co-citation analysis; B: Journals that overlay the visualization map.

macrophages", "10 cardiovascular disease", "11 diabetic wound repair", "12 mesenchymal stem cells", and "13 kokarnite". The values of each cluster mapping were > 0.6, indicating that the clusters were highly homogeneous and consistent. The keywords of the clusters were analyzed from the timeline (Figure 10B), which showed the research status of each keyword in each year and reflected the hotspot changes and trends in the research field. Figure 10C depicts the development and changes in research. Keyword emergence refers to the change rate of keyword frequency in a certain period, which can reflect the emerging or continuous research hotspots in the period and reflect the hotspot changes and trends in the field. The analysis yielded 25 key breakout words (Figure 11), with the highest outbreak intensity observed from 2013 to 2023 in adipose tissue (3.3), followed by bone marrow (3.25) and diabetic wound healing (2.87). Furthermore, the emergence of diabetic wound healing, diabetic wounds, nitric oxide, inhibition, and plasticity continued.

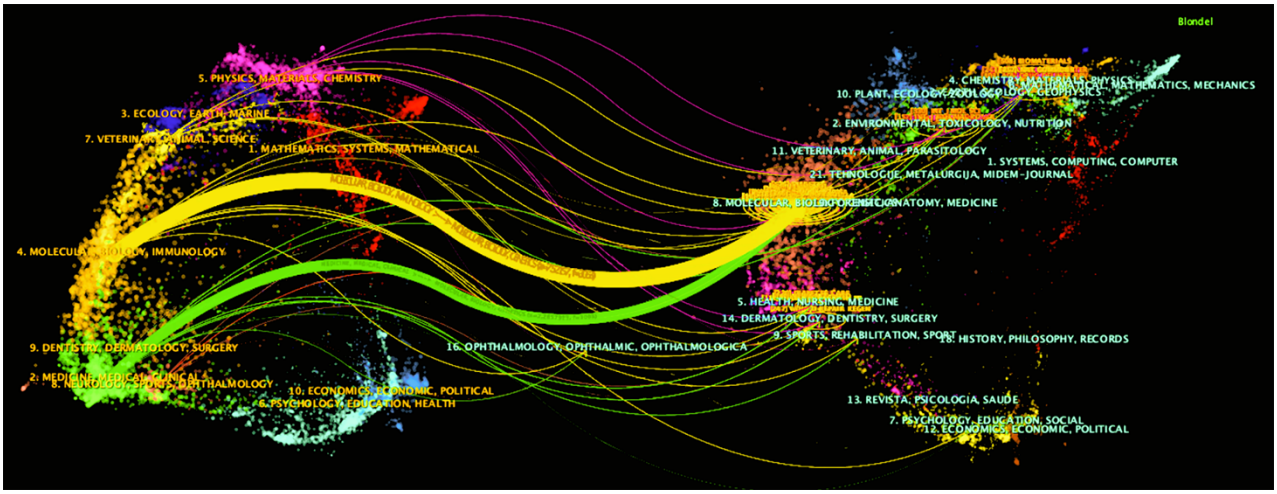


Figure 7 Dual-map overlay of journals that contributed to publications.

DISCUSSION

General information

Many studies have demonstrated that macrophages are highly multifunctional, displaying a highly functional state in a tissue- and time-dependent manner, with their phenotype determined by an environmental signaling network[24-26]. Macrophages are pivotal cells in human growth and development, exhibiting crucial homeostatic activity in almost all organ systems of the body[27]. Additionally, macrophages participate in all stages of tissue repair[28], and the repair response of macrophages to tissue injury must be well coordinated[29]. Thus, macrophage polarization plays a pivotal role in the healing process of DFUs and represents a potentially important therapeutic target. In this study, we employed literature visualization and analysis software to examine the literature on macrophage polarization and DFU healing between 2013 and 2023. Our analysis primarily focused on publication number analysis, co-occurrence analysis, and keyword analysis.

A gradual increase in publications about macrophage polarization in the field of DFU healing was observed from 2013 to 2023. The fitted curve indicated that the number of publications was on the rise. As shown in Figure 2, the publications in the last five years accounted for 81.75% of the total relevant publications, which suggests that this field is gradually gaining increasing attention from more researchers. It is therefore an important research direction. As shown in Table 1 and Figure 3, the United States was the first to concern this field, which may be related to the high degree of economic development in the United States and the wider scope of research. Although China started later in this field, it has developed rapidly and now become the top 1 in the number of publications and the intensity of cooperation. Five of the eight institutions with ≥ 10 publications are from China (Table 2) and five of the eight authors with ≥ 5 publications are from China (Table 3). With the increasing prevalence of diabetes in China, there are nearly 100 million diabetic patients, of which 15%-25% of the patients will develop foot ulcers in their lifetime. Therefore, DFU is increasingly recognized as an important health problem, and the research on DFUs has increased accordingly. However, despite the large number of articles published in China, the citation rate is generally not high. In China, most institutions with a large number of publications are in Beijing, Shanghai, Nanjing, and other economically developed areas, indicating that good discipline construction and sufficient and high-quality scientific research resources are related to the inheritance and development of traditional Chinese medicine and the support of national policies[30]. According to the network cooperation diagram (Figure 5), the cooperation among team members is close, but there are relatively few connections between different research teams, and the core author group in the research field has not been formed, which will affect the research development of this field. Therefore, continuous improvements in terms of government policies, research funding, and team cooperation are needed to conduct further in-depth and high-quality research in this field.

Hot spot and trend analysis

Hot spot analysis helps to explore research frontiers and trends in a specific field. Keywords summarize the main idea of the literature, representing the core and essence of the paper. The research hotspots related to macrophage polarization in DFU healing were analyzed according to keyword co-occurrence, clustering, and emergence. The keyword co-occurrence analysis revealed that macrophage polarization, inflammation, activation, wound healing, polarization, and expression were the most frequent (Table 5). Figure 9 indicates that these keywords include the main research objects and pathological mechanisms, which were important entry points for research. Figure 10 shows the following obtained keywords: "diabetic wounds, mesenchymal stem cells, reactive oxygen species, multifunctional hydrogels, neutrophil extracellular traps, diabetic retinopathy, endothelial cells, adipose tissue, inflammasome, macrophages, 10 cardiovascular disease, diabetic wound repair, mesenchymal stem cells, kokarnite". These keywords cover a wide range of topics, including research objects, complications, repair mechanisms, and treatments, reflecting the current research focus on macrophage polarization and DFU healing, especially the mechanism of inflammation and angiogenesis. Inflammation is

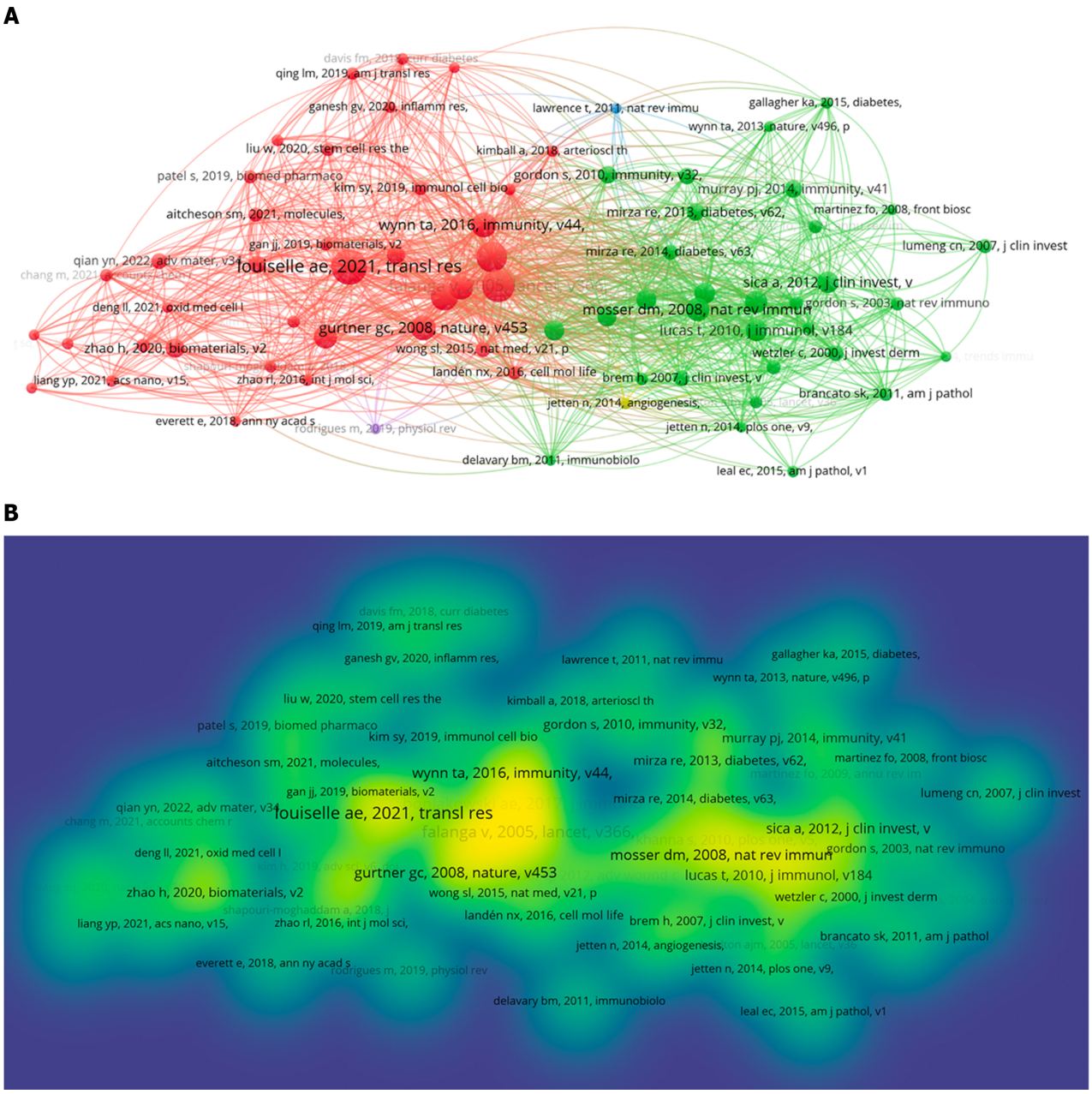


Figure 8 Co-cited literature map. A: VOSviewe-generated network visualization of journals' co-citation analysis; B: Journals overlaying the visualization map.

a critical stage of tissue repair, and macrophage polarization involves the balance between chronic inflammation and homeostasis, the underlying mechanism of which is not fully understood[31]. In addition, a strong and dynamic angiogenic response is essential for wound repair[32] as it can provide the required nutrients and oxygen. Macrophages can mediate angiogenesis and secrete regulatory factors to affect neointimal growth[33,34]. At present, it is widely accepted that the M2 phenotype is closely related to angiogenesis by secreting angiogenic growth factors, however, the specific mechanism remains unclarified[35].

Regulation of macrophage polarization

Keyword analysis revealed that "adipose tissue", "alternative activation", "dendritic cell", "insulin resistance", and "diet-induced obesity" first emerged in 2013 and have been studied for a long time (Figure 11). These keywords may have initially come from studies related to diabetes-related research and underpin the immunology and cell biology parts of the field. Since 2016, keywords such as "bone marrow", "adjustment, replacement, response, tissue repair", and other keywords related to the regulation of macrophage polarization in DFU healing have gradually emerged, which have become a topic of increasing concern. Regulation is the key to macrophage polarization and function[36]. Macrophage polarization is fundamental for tissue repair and maintaining homeostasis, in which macrophages develop different functional phenotypes in response to specific microenvironmental stimuli and signals. M1 macrophage polarization refers to the transformation of macrophages activated by LPS and Th1 cytokines (*e.g.*, interferon-gamma and TNF-α) into macrophage with characteristic surface phenotypes of toll-like receptor (TLR)-2, TLR-4, CD80, CD86, inducible nitric oxide synthase, and major histocompatibility complex class-II. M2 polarization is a response to downstream signals from

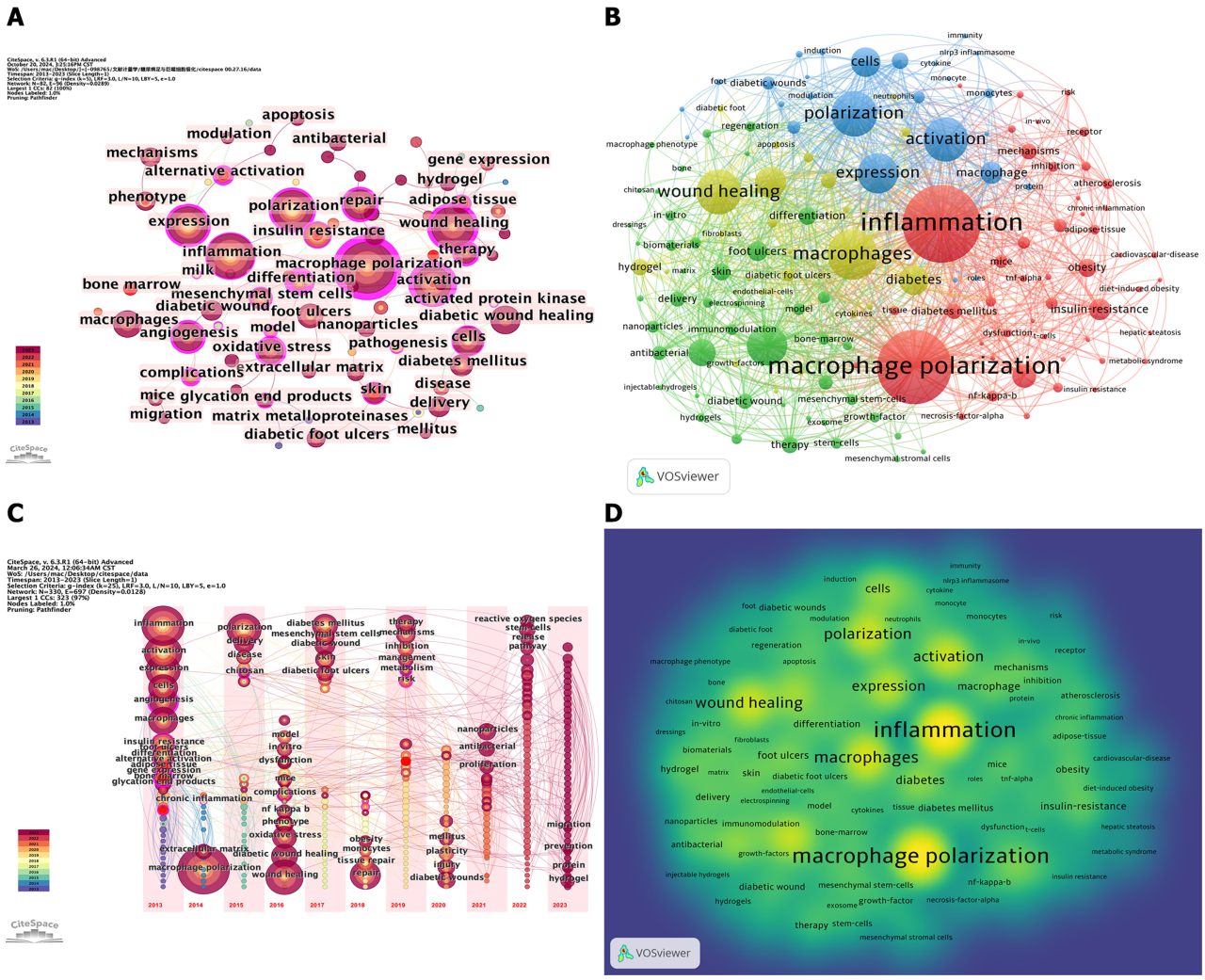
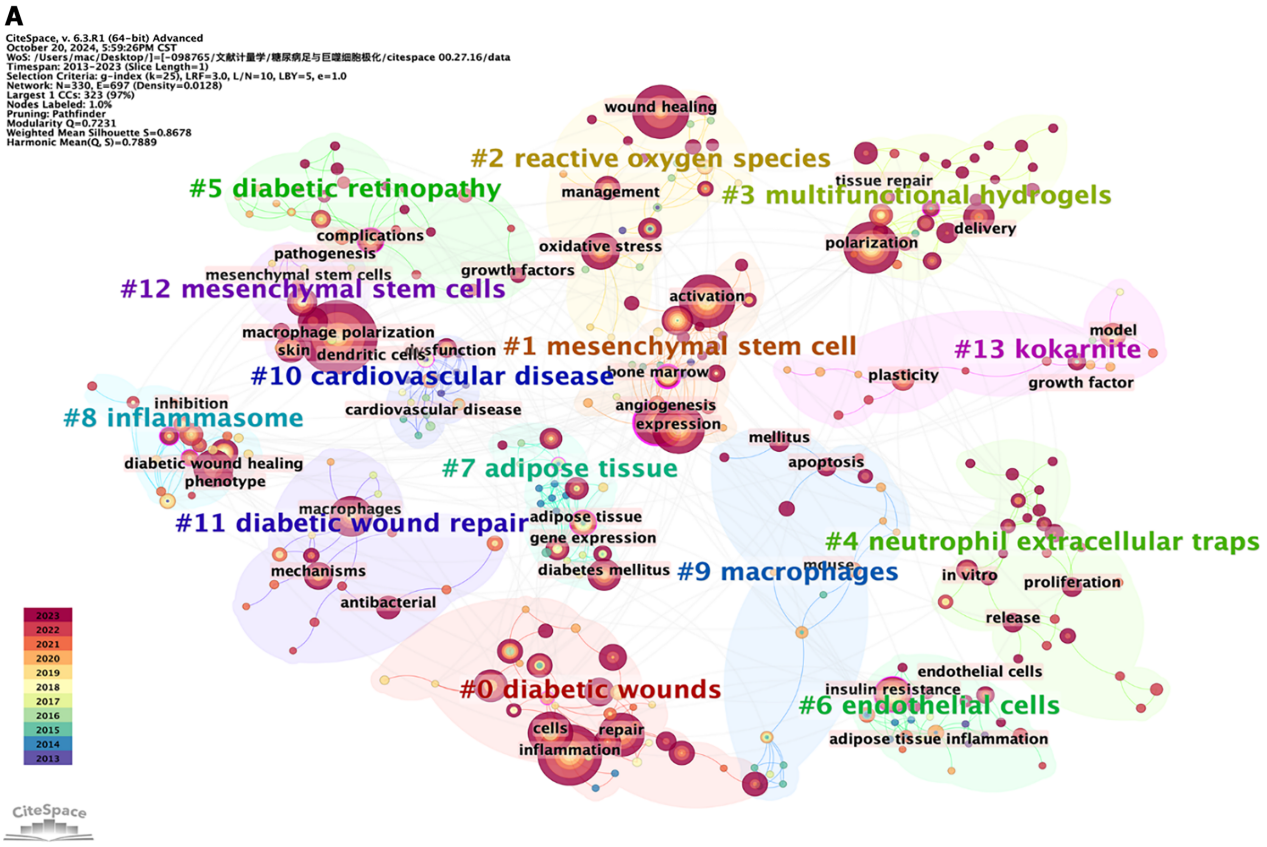


Figure 9 Keyword network graphs. A: A visualization graph of keywords; B: A time-zone map of keywords; C: VOSviewer-generated network visualization of keywords with a minimum of two occurrences; D: The top 10 keywords in terms of centrality.

cytokines such as IL-4, IL-13, IL-10, IL-33, and TGF-β, where IL-4 and IL-13 directly induce M2 macrophage activation, and other cells promote M2 macrophage activation by producing Th2 cytokines. The destiny of an organ during inflammation or injury hinges on the balance between M1/M2 macrophage polarization. When an organ is significantly influenced by infection or inflammation, macrophages initially present an M1 phenotype, releasing TNF-α, IL-1β, IL-12, and IL-23 in response to the stimulation. The prolonged presence of the M1 phase leads to tissue damage. Consequently, M2 macrophages secrete large amounts of IL-10 and TGF-β suppress inflammation, facilitate tissue repair, and remodeling, neovascularization, and maintain homeostasis. Some studies have unveiled the effect of curcumin and tanshinone II on the inflammation model of LPS-induced RAW 264.7 macrophages[37,38]. Curcumin can inhibit the nuclear factor (erythroid-derived 2)-like factor 2/antioxidant responsive element and nuclear factor kappa B (NF-κB) pathways, while tanshinone II can inhibit the TLR4-high mobility group box 1/CCAAT enhancer binding protein beta pathway to promote M2 phenotype polarization and reduce TNF-α and IL-1β levels. In addition, astragalus polysaccharide and astragaloside IV[39] can inhibit the LPS/high-glucose pathway and activate the nuclear factor (erythroid-derived 2)-like factor 2/heme oxygenase-1 pathway to effectively promote M2 polarization of diabetic macrophages. Geniposide can effectively promote the M2 polarization of macrophages in Apoe (-/-) mice and reduce C-X-C motif chemokine ligand 14 protein levels, but the specific pathway remains elusive[40]. Zizhu ointtiona traditional Chinese medicine compound, can activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway to repress inflammation and promote M2 polarization of macrophages, thus effectively promoting chronic wound healing by remodeling fibrous tissue[41].

Gene expression for macrophage polarization

This study also found that the keywords of cellular gene expression such as “expression”, “activation, repair, differentiation”, and “gene expression” have increased in recent years, and gene expression in DFU healing is becoming a hot topic. Macrophage polarization, initiation, and plasticity are dynamically regulated by complex gene networks and changes in signaling cascades through multilayered regulation of gene expression[42]. Macrophage membrane receptors initiate intracellular signaling pathways by sensing microenvironmental changes, accelerating nuclear translocation of transcription factors, and regulating downstream gene expression[43]. Currently, there are many transcription factors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Timespan: 2013-2023 (Slice Length=1)
Selection Criteria: g-index (k=25), LRF=3.0, L/N=10, LBY=5, e=1.0
Network: N=330, E=697 (Density=0.0128)
Largest 1 CCs: 323 (97%)
Nodes Labeled: 1.0%
Pruning: Pathfinder
Modularity Q=0.7231
Weighted Mean Silhouette S=0.8678
Harmonic Mean(Q, S)=0.7889
wound healing
#2 reactive oxygen species
#5 diabetic retinopathy
management
#3 multifunctional hydrogels
tissue repair
delivery
polarization
complications
pathogenesis
oxidative stress
mesenchymal stem cells
growth factors
#12 mesenchymal stem cells
activation
macrophage polarization
skin
dendritic cells
dysfunction
#1 mesenchymal stem cell
#13 kokarnite
model
#10 cardiovascular disease
bone marrow
plasticity
growth factor
inhibition
cardiovascular disease
angiogenesis
expression
#8 inflammasome
mellitus
diabetic wound healing
phenotype
#7 adipose tissue
apoptosis
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#11 diabetic wound repair
adipose tissue
gene expression
#4 neutrophil extracellular traps
mechanisms
diabetes mellitus
#9 macrophages
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release
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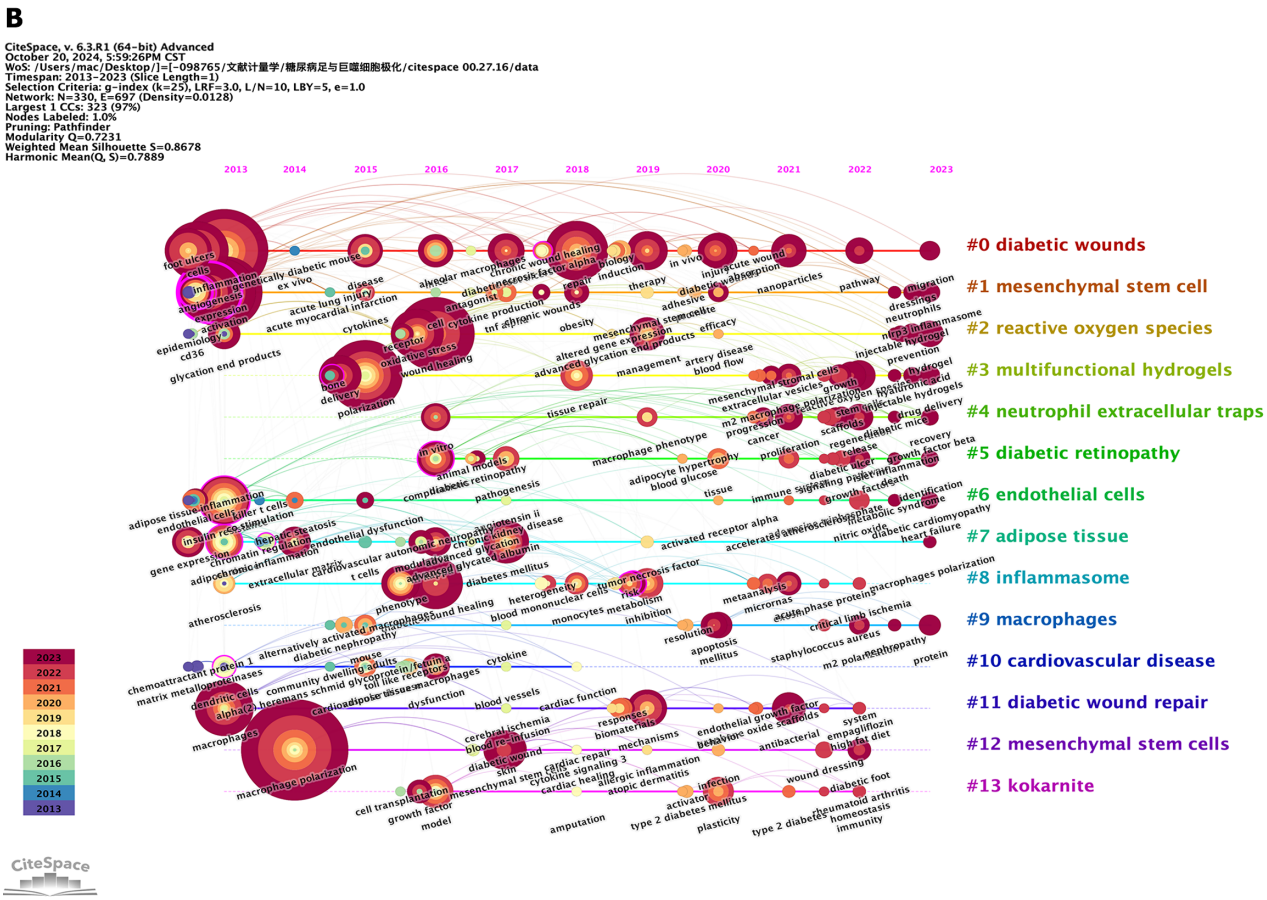
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Harmonic Mean(Q, S)=0.7889
2013
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#0 diabetic wounds
#1 mesenchymal stem cell
#2 reactive oxygen species
#3 multifunctional hydrogels
#4 neutrophil extracellular traps
#5 diabetic retinopathy
#6 endothelial cells
#7 adipose tissue
#8 inflammasome
#9 macrophages
#10 cardiovascular disease
#11 diabetic wound repair
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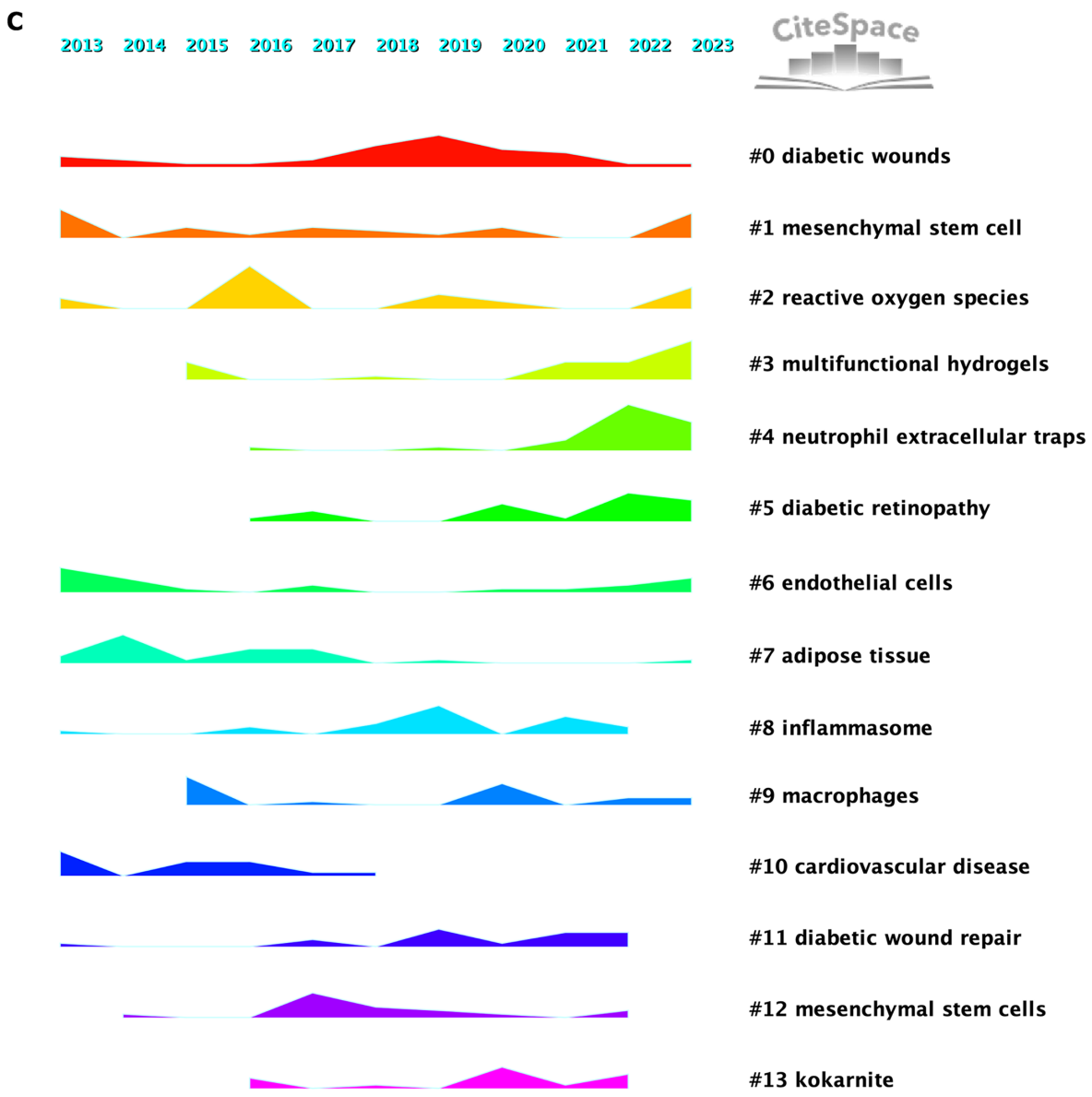

Figure 10 Keyword cluster analysis mapping. A: Citespace-based network visualization of keyword cluster analysis; B: Timeline map of keywords; C: The development and changes of keywords in research.

involved in macrophage polarization. NF-κB, signal transducer and activator of transcription (STAT)-1, and interferon regulatory factor 5 promote M1 polarization[44-46], while interferon regulatory factor 4, STAT-6, and peroxisome proliferator-activated receptor-gamma regulate M2 polarization[47,48]. LPS in M1-type macrophages activates several transcription factors, including mitogen-activated protein kinase, NF-κB, Jun N-terminal kinase, mitogen-activated protein kinase kinase/extracellular signal-regulated kinase, PI3K/AKT, and multiple signaling pathways through signal transduction and transcriptional activation[49-51]. In contrast, in IL-4-activated M2-type macrophages, it acts mainly through the activation of two independent signaling pathways, Janus kinase/STAT6 and PI3K/AKT/mammalian target of rapamycin complex[52,53]. Especially during ulcer healing and repair, non-coding regions of the genome, including microRNA, long non-coding RNA, nucleolar small RNA, PIWI-interacting RNA, and cyclic RNA, are also involved in macrophage activation and polarization at multiple levels, such as chromatin remodeling, post-transcriptional modification, and protein translation[54].

Development and application of novel wound materials

With the deepening of research, the rapid development of science and technology, and the strong demand for the transformation of achievements, the research hotspots have gradually shifted to biomedical research and application in recent years. This study found that the main keywords consisted of "mesenchymal stem cells", "adipose tissue", "gelatinized methyl acrylate", "conductive hydrogel", "adhesive tape", "adhesive tape", "adhesive tape", "adhesive tape", "adhesive tape", and "adhesive tape". Developing biomaterials capable of modulating macrophage polarization has become increasingly relevant for promoting the repair and regeneration of DFUs. Additionally, emerging methods for precisely modulating macrophage phenotypic shifts through pharmacological and gene therapies are gaining

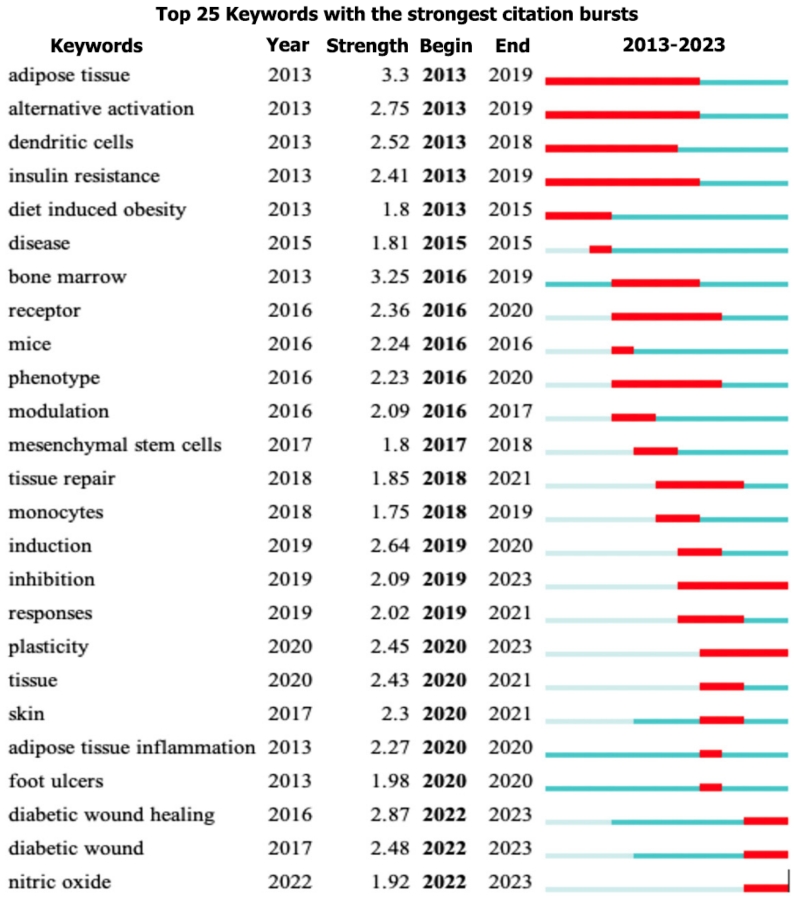

Figure 11 Keyword emergence map.

attention. As can be seen from keywords, there is a focus on biomaterials based on the immune system. The immune system plays an important role in wound healing and tissue repair, and biomaterial scaffolds are an emerging approach to drive immune-mediated tissue regeneration[55]. Bioscaffolds are associated with M2 macrophages during tissue regeneration. Sadtler *et al*[56] have shown that following traumatic tissue injury, bioscaffolds induce an immune microenvironment dependent on Th2 cells to reduce inflammation and support tissue regeneration. The accumulation of M1-type macrophages and excessive inflammation are common causes of delayed wound healing. Researchers promoted diabetic wound healing by developing a novel octanoic acid-based hybrid hydrogel dressing with intrinsic immunomodulatory properties[57]. Fu *et al*[58] prepared a natural hydrogel by mixing catechol and collagen and found that the hydrogel promoted the shift of M1-type macrophages to M2-type macrophages, shortened the inflammatory period, promoted neovascularization, and facilitated the healing of diabetic wounds. Chen *et al*[59] combined the silky fibroin with the vascular endothelium growth factor mimetic peptide KLTWQELYQLKYKGI to form a stable peptide hydrogel, which was found through *in vitro* and *in vivo* experiments to promote the shift of M1-type macrophages into M2-type macrophages, vascular neovascularization, the deposition of collagen, and the differentiation of keratinocytes, thus achieving wound healing. The advancement of novel therapeutic approaches derived from basic research, including drugs designed to target specific cell types or signaling pathways, as well as the application of bioengineering techniques to promote tissue repair, is anticipated to be a prominent field of interest.

Limitations of this study

The data in this study are stemmed from the WOSCC database, which provides high-quality literature data, so the results obtained are reliable. However, this study also has some limitations, mainly manifested in database selection, time point limitation, language bias, and missing literature due to non-indexed citations. Despite these limitations, this study provides an overall picture for researchers to formulate the next research strategies.

CONCLUSION

The present study utilized the bibliometric method to analyze the research on macrophage polarization in DFU healing from 2013 to 2023 in the WOSCC database. With the increasing incidence of diabetes and the implementation of related health strategies, the United States is the first to concern this field. Although China started later in this field, it now becomes the top 1 in the number of publications and the intensity of cooperation. Shanghai Jiao Tong University was the

research institution with the largest number of publications and the highest centrality, and the journal with the most publications was *Advanced Functional Materials*. The research hotspots mainly include regulation, macrophage activation, gene expression, wound tissue repair, and new wound materials. The results revealed the high-influence countries and institutions, journals, references, research hotspots, key research areas, and future research directions of macrophage polarization on DFU healing.

FOOTNOTES

Author contributions: Sun L conceived and designed the study; Zhang YW and Sun L participated in data processing and statistical analysis; Wang YN and Zhan SY supervised the review of the study; Zhang YW, Sun L, Wang YN, and Zhang SY drafted the manuscript and contributed to data analysis and interpretation; and all authors seriously revised and approved the final manuscript.

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