Scientific trends and knowledge structures of exosomes from macrophages: a bibliometric analysis

Yi Liu
School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002

Bowen Zheng
School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002

Yuan Zhong
School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002

Yi Liu (liuyi@cmu.edu.cn)
School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002

Article

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Abstract

Background:

Exosomes from macrophages present unique roles in body systems and regulate inflammation or physiological processes. A bibliometric analysis may reveal topic patterns of macrophage-derived exosomes that can be used to investigate future research.

Objectives:

The aim of this study was to explore the research trends and knowledge structures of macrophage-derived exosomes during past 11years.

Materials and methods:

Literature related to exosomes from macrophages was scanned in the PubMed database, with a period of 2011 to 2021. The analysis retrieved 2457 records and performed high-frequency major MESH terms/MESH subheadings extraction, biclustering analysis, strategy map analysis, and social network analysis.

Results:

Cluster analysis yielded 5 categories in which the rather mature clusters in the past 11 years are mainly about bioengineering, therapeutic methods, and osteoclast-related metabolism. Tumor-associated macrophages and exosomes, as well as the regulation of the immune system, are discussed in Cluster 1 and 2, which possess great potential for advancement. Cluster 3 focuses on the interaction of mesenchymal stem cell exosomes with macrophage cytology. Extracellular Vesicles/immunology; Exosomes/transplantation; Mesenchymal Stem Cells/cytology; and other terms around the network are all possible future research hotspots, according to the social network analysis.

Conclusion:

Research topics such as tumor-associated exosomes, exosome physiology, and exosomes/transplantation still deserve deep research. Further research should expand on new topics such as exosomes and macrophages in the tumor environment, exosomes from mesenchymal stem cells, and cell-free therapy.

1 Introduction

Macrophages are the main effector cells of human innate immunity. Under diverse stimuli, macrophages will be polarized into traditionally activated macrophages (M1) and alternatively activated macrophages (M2). Exosomes are extracellular vesicles (EVs) with a diameter of 50–150 nm. They transport proteins and miRNAs across cells by delivering them to target cells and modifying their activity[1]. Exosomes

generated from macrophages can mimic the function of their parent cells, and influence many body systems via regulating inflammation and related pathways. Metabolism and therapeutic functions of exosomes from macrophages have received a lot of attention. However, few studies give a comprehensive review of the research and knowledge base. Bibliometrics is a quantitative research tool that could monitor and propose hot scientific domains from publications on a specific topic. This work uses the bibliometrics approach to examine the literature on exosomes from macrophages over the last 11 years to reveal topic patterns and knowledge structures.

Co-word analysis calculates the frequency at which two words appear in the same article, which can be used to highlight existing research topics. The more frequently the two words appear together, the more closely the two terms are related. A large number of co-occurring terms emphasize research topics among a research area. Cluster analysis can identify and study research topics, with strategy diagrams representing each cluster's development trend. Social network analysis (SNA) can intuitively characterize the distribution and interactions of the co-occurring terms. In this work, we chose literature related to exosomes from macrophages and combined co-word analysis, cluster analysis, SNA analysis, and strategy map to disclose the research foundation and broad trends.

2 Materials And Methods

2.1 Data collection

We searched the PubMed database for literature from 2011 to 2021 using the search strategy “(((exosome) OR (EVs)) OR (extracellular vesicles)) AND (macrophage)”, without language or species restrictions. MEDLINE is one of the most authoritative abstract medical literature databases in the world, with a wide range and friendly interface. A total of 2457 literature records were searched by two researchers independently, and the results were stored in the "PubMed" format.

2.2 Data extraction

The Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) software developed by Professor Cui Lei of China Medical University was utilized to extract the necessary data in the PubMed format document[2], including publication year, first author, publication country, journal, major MESH terms/MESH subheadings. We applied the H-index method to perform word frequency statistics to filter high-frequency main MeSH terms/subheadings, that is, first extract the major MESH terms/MESH subheadings of all articles and sort the terms according to the frequency of occurrence (h)[3]. Words whose frequency is greater than or equal to their order number (h) are defined as high-frequency main MeSH terms/subheadings. BICOMB uses the PMID number (PubMed Unique Identifier) of the article as the first column and the high-frequency MESH terms as the first row to construct the term-source matrix. Co-occurrence matrix can also be constructed for rows and columns in high-frequency MESH terms. Both matrices were used for subsequent analysis.

2.3 Biclustering analysis

The term-source matrix acquired above was imported into gCLUTO (Graphical CLUstering Toolkit, version 1.0, USA) for biclustering analysis[4]. We clustered several times until we reached the minimum average similarity between classes (Esim) and the maximum intra-class similarity (ISIMM) value, which generated the heatmap and the peak map to visualize the content of matrix data. In the heatmap, the high-frequency MESH terms are depicted in rows, and the clustering results are grouped into several primary columns. The bottom of the matrix shows the PMID for each article. The color depth of the grid (white to red) shows the relative frequency of the MESH terms in the article, with darker red representing greater frequency. In the peak map, the different peaks signify separate clusters, the height of a mountain denotes the internal similarity of its cluster, whilst the volume of a mountain represents the number of major MESH terms inside. The hue of the peaks represents the standard deviation inside the cluster, with red signifying low deviation and blue indicating large variance.

2.4 Strategic diagram

According to the co-occurrence matrix of high-frequency MESH words, the calculation of the centrality (external cohesion index, which represents the interaction of a term with other terms) and the density (internal cohesion index, the closeness of the clustering internal subject terms) is performed for each cluster[5]. The centrality and density are represented by the X-axis and the Y-axis, respectively, and the findings of biclustering analysis are classified according to the four quadrants separated by the two axes. Using EXCEL software to build a coordinate graph, the clusters in the first quadrant have high density and high centripetal degree, while the categories in the third quadrant have low density and low centripetal degree. This graphic can be used to characterize the completeness of the cluster and scientific trends.

2.5 Social network analysis

SNA analysis is a mathematical network of words constructed from co-occurrence matrix derived from high-frequency main MeSH terms/subheadings[6]. This type of two-dimensional network can intuitively express term connections and prompt the domain's knowledge structure. We obtained and calculated the value of each MESH term node using UCINET Social Network Analysis Software Version 6 (Analytic Technologies, USA). Then we performed network analysis with NetDraw Network Visualization (Analytic Technologies, KY, USA) to provide the position of words in the network, as well as centrality data.

3 Results

3.1 Distribution characteristics of relevant literature

We searched the literature related to macrophage-derived exosomes in the past 11 years and created statistical mappings of the descriptive data (Fig. 1). In Fig. 1A, the number of articles published per year has shown a growing trend, and the rise has been more rapid in the previous three years, reaching 755 articles in 2020. The most popular journal was Frontiers in immunology (110, 4.41%) (Impact Factor (IF) = 7.561, 2020), followed by Scientific reports (65, 2.61%) (Impact Factor (IF) = 4.379, 2020) and International journal of molecular sciences (62, 2.49%) (Impact Factor (IF) = 5.923,2020) (Fig. 1B). Wang

Y was the most productive author, with a total of 93 counts. The top 10 authors are listed in Fig. 1C. The United States published the most relevant articles (333, 38.0%), followed by England (192, 21.9%) and Netherlands (149, 16.9%) (Fig. 1D).

3.2 Research hot spots identified by MeSH term clusters

Through the H index method, we found a total of 27 high-frequency main MeSH terms/subheadings (cumulative frequency 26.19%) (Table 1). These terms are considered research hotspots in the field of exosomes from macrophages. We built the term-source matrix and co-occurrence matrix and recognized the high-frequency MeSH terms/subheadings into five clusters with bicluster analysis (Fig. 2A and B). In the peak map, cluster 0 and cluster 4 were represented in red, indicating that their internal similarity was relatively high. The other categories were green or blue, suggesting a higher deviation. The results of the cluster analysis were provided by a heatmap (Table 2, Fig. 2B), in which the left-hand hierarchical tree illustrates the links between high-frequency MESH terms and the top hierarchical tree shows the connections between articles. By evaluating the literature suggested by the red area, we summarized the 27 high-frequency MESH terms and five clusters into 10 research hotspots (Table 2). Supplementary Table 1 shows representative articles for clusters provided by gCLUTO program with Esim and Isim values for each cluster.

Table 1
High-frequency MeSH terms/MeSH subheadings from papers on exosomes from macrophages

Rank	Major MeSH terms/ MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
1	Exosomes/metabolism	372	4.2359	4.2359
2	Macrophages/metabolism	295	3.3591	7.5951
3	Extracellular Vesicles/metabolism	235	2.6759	10.2710
4	MicroRNAs/metabolism	184	2.0952	12.3662
5	Macrophages/immunology	179	2.0383	14.4045
6	MicroRNAs/genetics	143	1.6283	16.0328
7	Cell-Derived Microparticles/metabolism	90	1.0248	17.0576
8	Mesenchymal Stem Cells/metabolism	80	0.9110	17.9686
9	Extracellular Vesicles/immunology	80	0.9110	18.8795
10	Exosomes/immunology	70	0.7971	19.6766
11	Exosomes/genetics	48	0.5466	20.2232
12	Inflammation/metabolism	40	0.4555	20.6787
13	Cell-Derived Microparticles/immunology	38	0.4327	21.1114
14	Macrophages/drug effects	37	0.4213	21.5327
15	Macrophages/cytology	36	0.4099	21.9426
16	Exosomes/transplantation	35	0.3985	22.3412
17	Macrophages/physiology	34	0.3872	22.7283
18	Exosomes/physiology	34	0.3872	23.1155
19	Exosomes/chemistry	33	0.3758	23.4912
20	Mesenchymal Stem Cells/cytology	32	0.3644	23.8556
21	Macrophages/pathology	32	0.3644	24.2200
22	Extracellular Vesicles/chemistry	31	0.3530	24.5730
23	Osteoclasts/metabolism	30	0.3416	24.9146
24	Neoplasms/immunology	29	0.3302	25.2448
25	Tumor Microenvironment/immunology	29	0.3302	25.5750
26	Extracellular Vesicles/physiology	27	0.3074	25.8825

Rank	Major MeSH terms/ MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
27	Neoplasms/metabolism	27	0.3074	26.1899

Table 2
Cluster analysis of high-frequency major MeSH terms/MESH subheadings

Cluster	Number	MESH terms	Cluster analysis
0	6, 11, 21, 22	Macrophages/pathology Extracellular Vesicles/chemistry MicroRNAs/genetics Exosomes/genetics	1. Exosome properties and bioengineering; 2. Exosome microRNA (miRNA) contents and regulation
1	5, 9, 10, 13 24, 25	Tumor Microenvironment/immunology Macrophages/immunology Extracellular Vesicles/immunology Exosomes/immunology Cell-Derived Microparticles/immunology Neoplasms/immunology	1. Tumor-associated macrophages (TAMs), Tumor-derived exosomes (TEXs) and tumor development; 2. Exosomes on immune regulation
2	14, 17, 18, 19, 26	Macrophages/drug effects Macrophages/physiology Exosomes/physiology Exosomes/chemistry Extracellular Vesicles/physiology	1. Exosomes physiology 2. Exosomes and cell-free therapy
3	8, 15, 16, 20 27	Mesenchymal Stem Cells/metabolism Macrophages/cytology Exosomes/transplantation Mesenchymal Stem Cells/cytology Neoplasms/metabolism	1. Macrophages cytology; 2. Mesenchymal stem cell (MSC) derived exosomes and metabolism

Cluster	Number	MESH terms	Cluster analysis
4	1, 2, 3, 4, 7, 12 23	Exosomes/metabolism Macrophages/metabolism Extracellular Vesicles/metabolism MicroRNAs/metabolism Cell-Derived Microparticles/metabolism Inflammation/metabolism Osteoclasts/metabolism	1. Inflammation metabolism; 2. Osteoclasts metabolism and signal transduction

3.3 Strategy diagram and scientific trends of macrophage-derived exosomes

Strategy diagram is a graphic that explains cohesiveness inside and outside[7,8]. We specified the rank and cluster for each MeSH term and calculated the word connections innate cluster and other clusters to form coordinates of each cluster. Cluster 0 and cluster 4 were positioned in the first quadrant, with high density and high centripetal degree, implying that these themes are well-researched. Cluster 1 and cluster 2 were positioned in the third quadrant, signifying rather peripheral and underdeveloped themes. Cluster 3 was located in the fourth quadrant which represents the core and undeveloped topics. We utilized colored dots to indicate different clusters, the more terms contained, the larger the size (Fig. 2C).

3.4 Social network and knowledge structure of exosomes from macrophages

Bicluster analysis or heat map can provide the overall distribution features of clusters, but cannot disclose the relationship between MESH terms. Social network analysis, however, can intuitively depict the links between terms[9]. We used the 27 high-frequency main MeSH terms/subheadings above to develop the knowledge structure of exosomes from macrophages and then build the network. As seen in Fig. 3, the network consisted of nodes and lines to explain the closeness, betweenness, and degree of every MeSH terms/MESH subheadings. Nodes represented MESH terms while the line shows the frequency of the two related words appearing together. The greater the frequency, the thicker the line. A total of ten terms (Supplementary Table 2) whose degree centrality was greater than the average of 13.259, indicating that they can influence the network effectively.

Table 3
Individual centrality of exosomes from macrophages

Rank	Major MeSH terms/MeSH subheadings	Degree	Betweenness	Closeness
1	Exosomes/metabolism	22	17.951	24
2	Macrophages/metabolism	24	28.785	25
3	Extracellular Vesicles/metabolism	17	9.177	21.5
4	MicroRNAs/metabolism	23	23.296	24.5
5	Macrophages/immunology	20	14.272	23
6	MicroRNAs/genetics	23	20.964	24.5
7	Cell-Derived Microparticles/metabolism	14	4.237	20
8	Mesenchymal Stem Cells/metabolism	16	6.086	21
9	Extracellular Vesicles/immunology	10	2.531	18
10	Exosomes/immunology	12	3.899	19
11	Exosomes/genetics	11	2.584	18.5
12	Inflammation/metabolism	11	1.748	18.5
13	Cell-Derived Microparticles/immunology	9	1.827	17.5
14	Macrophages/drug effects	12	4.213	19
15	Macrophages/cytology	14	4.48	20
16	Exosomes/transplantation	9	0.535	17.5
17	Macrophages/physiology	10	3.293	18
18	Exosomes/physiology	8	1.581	17
19	Exosomes/chemistry	9	1.304	17.5
20	Mesenchymal Stem Cells/cytology	13	4.744	19.5
21	Macrophages/pathology	8	0.425	17
22	Extracellular Vesicles/chemistry	8	0.736	17
23	Osteoclasts/metabolism	7	0.225	16.5
24	Neoplasms/immunology	13	4.081	19.5
25	Tumor Microenvironment/immunology	12	3.702	19
26	Extracellular Vesicles/physiology	9	1.92	17.5
27	Neoplasms/metabolism	14	3.402	20

"Macrophages/metabolism" had the highest betweenness centrality (28.785) indicating that it had the biggest mediating influence on the network. Terms around the network had larger growth potential and were predicted to become rising research hotpots. Considering the distribution of each cluster in the strategy map, we have selected the following 8 hotspots (pink boxes), including Extracellular Vesicles/immunology; Exosomes/transplantation; Mesenchymal Stem Cells/cytology; Extracellular Vesicles/physiology; Exosomes/chemistry; Exosomes/physiology; Exosomes/immunology; Cell-Derived Microparticles/immunology.

4 Discussion

MeSH terms provide the most accurate representation of the topic of the literature. This research concluded the topics and subject trends of exosomes from macrophages using high-frequency major MESH terms/MESH subheadings. Exosomes/metabolism, Macrophages/metabolism are the most popular MESH phrases. We evaluated the distribution characteristics of related literature with BICOMB software and refined 5 clusters (10 research hotspots) with biclustering analysis. Then we created coordinates for each category in the strategy map and utilized social network analysis to uncover knowledge structures.

In the past 11 years, research connected to exosomes from macrophages had been boomed. From the standpoint of journals, Frontiers in immunology, Scientific reports, and International journal of molecular sciences are the top three journals, which are anticipated to continue to publish high-quality related publications in the future. Authors such as Wang Y are particularly prolific authors in the discipline. In national statistics, the United States published the most papers, reaching 333. Other countries including the UK and the Netherlands are also productive(Fig. 1).

Clusters 0 and 4 are found in the first quadrant of the strategy map, signifying that these prominent issues are relatively mature and well researched (Fig. 2C). Modifying exosome surface characteristics such as anchored proteins (Bioengineered EVs) could decrease pro-inflammatory cytokine responses or regulate other physiological processes [10]. Exosomes from macrophages reduce heat hyperalgesia in a mouse model of inflammatory pain, implying an immunoprotective signal against inflammation[11].

In bone tissue, tissue-resident macrophages coexist alongside bone tissue cells altering bone metabolism. The activity of osteoclasts links to different diseases and signaling pathways, and mature osteoclasts (mOCs) can be created by stimulating bone marrow macrophages with receptor activator of nuclear factor-b ligand (RANKL) [12]. Osteosarcoma cells release exosomal miR-501-3p, which can induce osteoclast formation via the PTEN/PI3K/Akt signaling pathway[13].

Clusters 1 and 2 are in the third quadrant and represent less mature themes that will require additional research in the future.

The interplay of macrophages with the tumor microenvironment(TME) has gotten a lot of interest. EVs are one of the important components of communication between tumor cells or the microenvironment[14], which can promote or suppress tumor development, invasion, and metastasis. The miRNAs or long non-coding RNAs contained in EVs can act as the mediator. Exosomes from retinoblastoma cells are capable of increasing levels of monocyte chemotactic protein 1 (C-C motif chemokine ligand 2), as well as miR-92a, miR-20a, miR-129a, and miR-17 to mediate tumor progression[15]. THP-1-induced macrophage-derived exosomes could facilitate osteosarcoma cell progression by transmitting miR-29a to osteosarcoma cells[16]. Tumor-derived exosomes (TEXs) have been engineered to aid tumor evasion and promote the differentiation of macrophages to adjust the immune response. Known as tumor-associated macrophages (TAMs), M2 macrophages promote cancer progression and metastasis, while M1 macrophages produce cytokines such as interleukin-12 (IL-12) and inhibit tumor growth[1]. Exosome quantification is often based on protein content, fluorescent labeling approaches are more precise and offer the added benefit of following EVs in vivo[17].

Exosomes influence macrophage activity, resulting in polarity shifts that make exosomes a target for immune modulation[18]. Neutrophil-derived exosomes regulate macrophage behavior, and macrophages no longer trigger fibroblast-like synoviocytes after intra-articular injection of neutrophil-derived exosomes. This may aid in the control of synovial inflammation[19]. Exosomes purified from community-associated methicillin-resistant S. aureus strains can be internalized by human macrophages, which promoting and caspase-1 activation[20]. Exosomes are cell-free fluid with immunomodulation and vaccination potential. The advantages of exosomes, on the other hand, are not absolute. Conforti discovered that IL-10 and tgf1 levels in T and B cells were much higher, but the human granulocyte-macrophage colony-stimulating factor (GM-CSF) levels were significantly lower. In vitro, the effects of exosomes alone on T cell proliferation and antibody production were not significantly increased[21]. More prospective studies are required to assess exosome relative merits.

Exosome membranes can effectively shield their contents from destruction, and their immunogenicity is minimal due to the small number of membrane-bound proteins that can dodge immune reactions. They are great drug carriers with enormous potential as cell-free players in bone disorders, inflammatory management, targeted therapy, and other applications[22]. Exosomes from metastatic breast cancer 4t1 cells can influence hepatic macrophage function and potentially minimize the negative effects of chemotherapy drugs[23]. MSC exosomes can mediate and stimulate tissue healing, and express a variety of immunomodulatory rather than immunosuppressive factors[24]. Inflammation is a critical regulating point in disorders that influence bone metabolism, such as diabetes. Zhang[25] found that exosomes produced from adipose-derived mesenchymal stem cells (AD-MSCs) may block osteoclast release of IL-1 and IL-18 and reverse bone loss in diabetic rats. This has the potential to be a cell-free treatment for diabetic bone loss. Osteopontin (OPN) is a protein that regulates bone remodeling and tissue debridement. Investing in exosome-based drug delivery systems in the future could be a viable

therapeutic approach; however, additional study on its components and physiology is required to clarify the currently unknown mechanism.

Cluster 3 is a mature issue in the fourth quadrant with potentials. The phenotypic transition of macrophages is currently a popular issue. Changes in the milieu of disease-site resident macrophage subsets may limit subtype transition by reflecting changes in their unique microenvironment. To increase the roles of resident macrophages in tissues, researchers have used macrophage exosomes or other methods to promote phenotype switch. The composition and content of exosomes can be influenced by changes in macrophage activity. Exosome synthesis by monocytes and macrophages is increased by alcohol, and exosome communication between immune cells is affected[26]. Exosomes produced by phagocytes have been shown to improve M2 polarization in microglia and induce neuroprotection[27]. More research is needed to better understand how macrophage subtype and microenvironment influence disease development. Studies have shown that exosomes from mesenchymal stem cells improve myocardial damage after myocardial infarction by boosting the transition of macrophages to M2 polarity[28]. Exosomes released by bone marrow mesenchymal stem cells also helped animals with respiratory problems[29].

According to the social network analysis results (Fig. 3), the mature topic "Macrophages/metabolism" at the network's core is the mature topic with the highest centrality value, the most links with surrounding terms, and the most influence on the network. The pink boxes on the edge represented new research hotspots, including Extracellular Vesicles/immunology; Exosomes/transplantation; Mesenchymal Stem Cells/cytology; Extracellular Vesicles/physiology; Exosomes/chemistry; Exosomes/physiology; Exosomes/immunology; Cell-Derived Microparticles/immunology.

This work uses objective bibliometric approaches to demonstrate subjects for scholars to investigate additionally, although there are still some limitations. First, we only selected the literature in the PubMed database; there may be differences in the other database. Second, the co-word analysis concentrates on high-frequency words while ignoring low-frequency words, which should be considered in future bibliometric studies for statistical purposes.

5 Conclusion

The main MeSH terms/subheadings of the literature linked to exosomes from macrophages were identified with bibliometric analysis. We summarized 5 categories and 10 research hotspots with biclustering analysis, performed strategy map analysis, and finally created social network analysis from the MESH terms. We revealed the distribution of literature related to exosomes from macrophages by sorting countries, journals, authors, and publications. The therapeutic potential of exosomes, as well as exosome-related bioengineering, are well-studied and mature components, although the interaction between tumor and macrophage related exosomes, exosome-mediated immune control, and cytology have yet to be explored. Extracellular Vesicles/immunology, Exosomes/transplantation, and

Mesenchymal Stem Cells/cytology are examples of points that can provide useful knowledge and direction for future research.

Declarations

Author's statement

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Author contribution

Prof.YL contributed to the conception of this manuscript. YL, BZ, and YZ conducted data collection and cleaning, YL completed the manuscript, and Prof. YL reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest

Authors state no conflict of interest.

Data availability statements

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

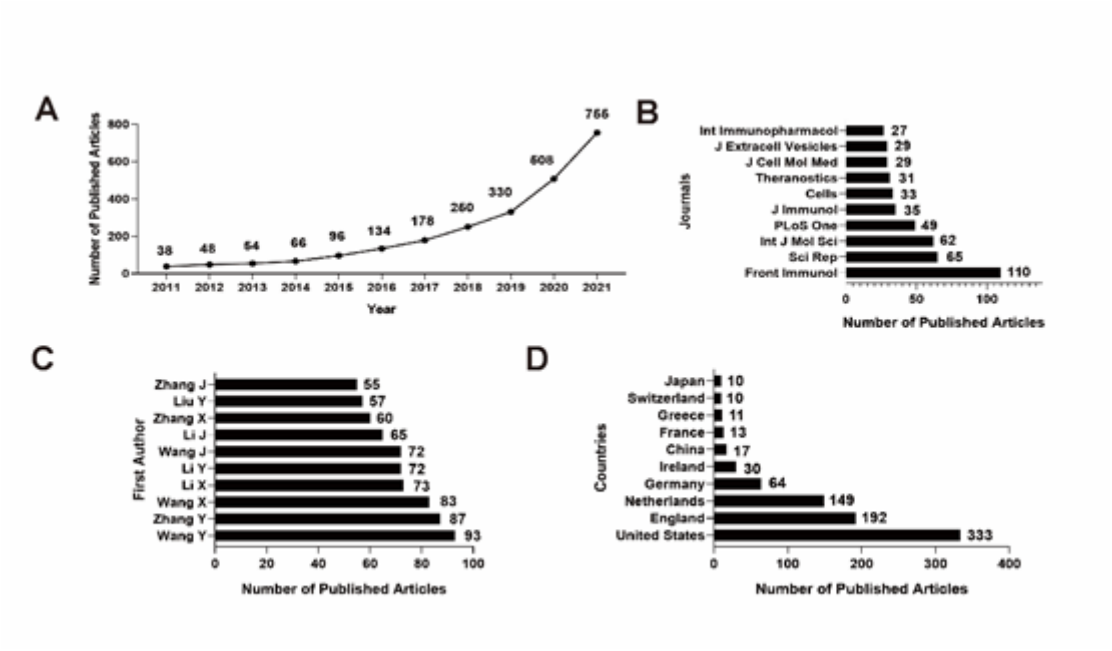

Figure 1

Distribution characteristics of relevant research. (A) Numbers of published articles from 2011 to 2021. (B) Numbers of published articles from the top 10 journals from 2011 to 2021. (C) Numbers of published articles from the top 10 authors from 2011 to 2021. (D) Numbers of published articles from the top 10 countries from 2010 to 2021.

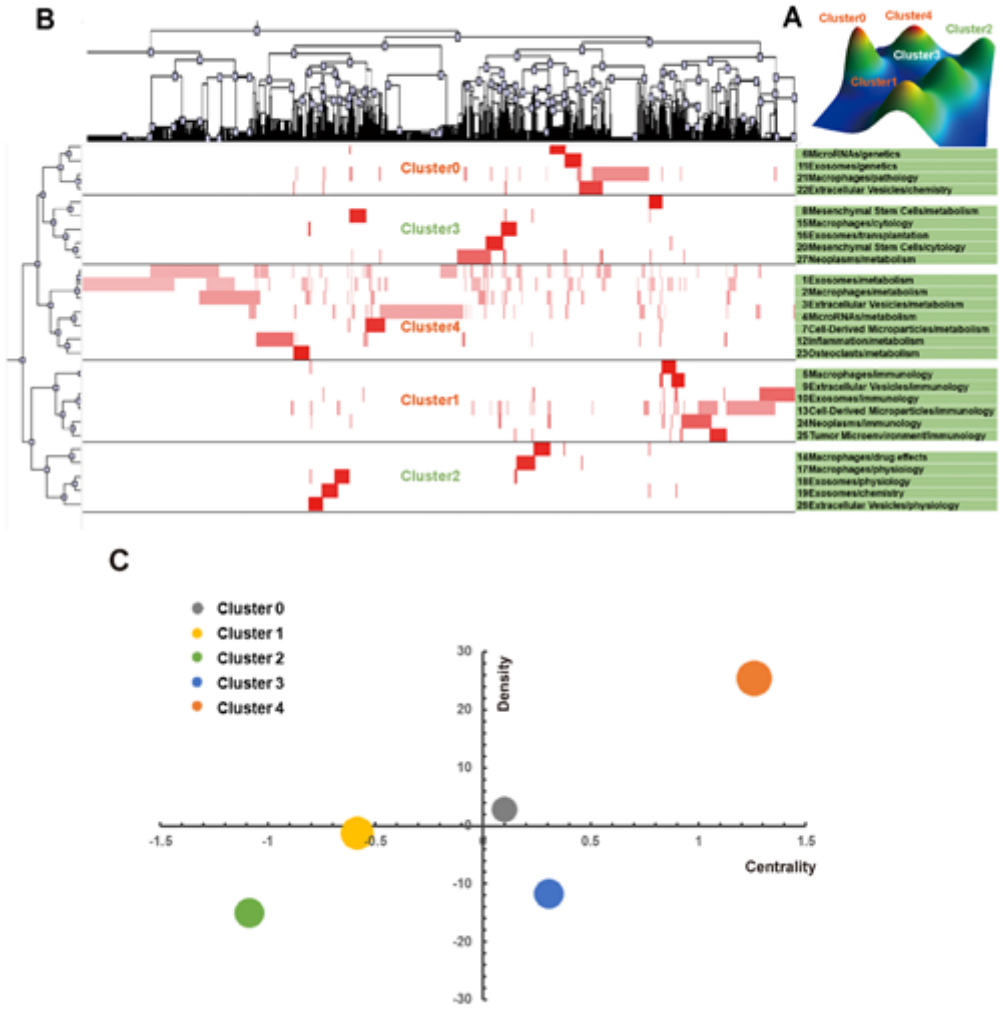

Figure 2

Biclustering analysis of 27 high-frequency major MESH terms/MESH subheadings of relevant research from 2011 to 2021. (A) Peak map. (B) Heat map. (C) Strategic diagram. Each cluster is represented by dots of different colors. The size of the dots is proportional to the number of MESH terms in each cluster.

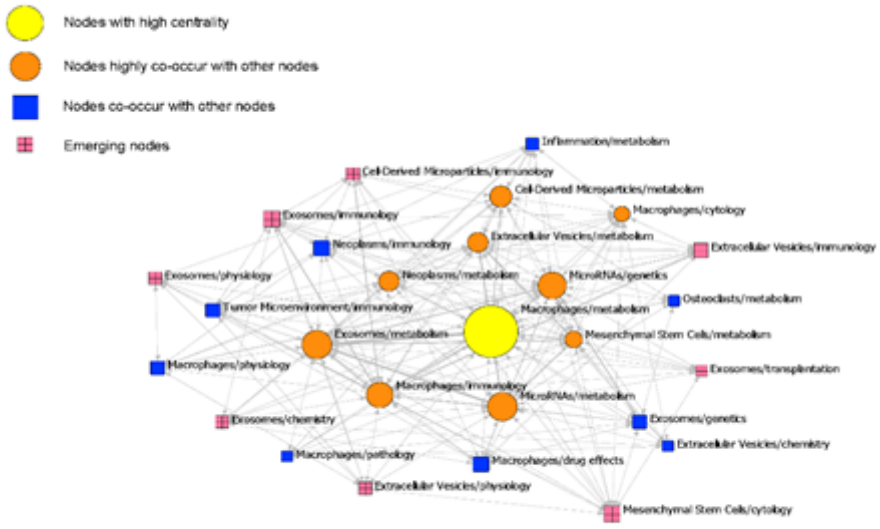

Figure 3

SNA for high-frequency major MeSH terms / MeSH subheadings on relevant research. The network parameters (degree, betweenness, and closeness) are listed in Table 3. The word with the greatest betweenness centrality is represented by the yellow dot in the middle. Words with degree centrality greater than average are highlighted in orange. Pink boxes indicate emerging hotspots throughout the network.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx