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RESEARCH

Effects of exosomes and inflammatory response on tumor: a bibliometrics study and visualization analysis via CiteSpace and VOSviewer

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Abstract

Background Tumor is a new organism formed by abnormal hyperplasia of local tissue cells under the action of various tumorigenic factors. Inflammation plays a decisive role in inducing tumorigenesis, promoting tumor development, invasion and migration. More and more evidence indicate that exosomes are involved in regulating the formation of tumor microenvironment in the process of proinflammatory carcinogenesis, leading to the stimulation of anti-tumor immune response or systemic immunosuppression, and exosomes play a crucial role in the development of tumor.

Methods The articles on tumor-derived exosomes and inflammatory responses from January 2005 to January 2024 were collected through Web of Science (WOS), and the inclusion criteria were "Article", "Review Article" and "Early Access". Articles obtained after excluding "Book Chapters", "Editorial Material", "Proceeding Paper", "Meeting Abstract" and "Retracted Publication". Bibliometrics and visualization analysis were carried out on the obtained articles using CiteSpace6.2.R6 and VOSviewer1.6.20.

Results Total of 703 articles were included. The number of published documents showed a fluctuating growth trend year by year. A total of 61 countries have participated in the research on the effects of exosomes and inflammatory responses on tumors, among which China and the United States have the largest influence in this field. The obtained articles have been published in 60 journals around the world, among which PLOS ONE and NAT REV IMMUNOL are the journals with the most published articles and the highest co-citations respectively. The article from French author THERY C was cited the most (202 times). As a major researcher on the basic function of exosomes, THERY C established the gold standard for extraction, separation and identification of exosomes, and found that exosomes promote tumor metastasis through direct regulation of miRNA. Her research has had a huge impact on the field. Keyword co-occurrence analysis indicate that extracellular vesicles, inflammation, cancer, miRNAs, mesenchymal stem cells, drug delivery, gastric cancer and circulating endothelial microparticles are the research hotspot at present stage. The main keywords of the cluster analysis show that extracellular vesicles, human papilloma virus, myeloid cells, tumor macro-environment are the current research hotspots and frontier. The research hotspots have developed over time from the time chart of keywords and clustering, especially after 2016, exosomes have established extensive links with drug delivery, cancer treatment, inflammatory response and other fields. Tumor-derived exosomes stimulate receptor cells to secrete pro-inflammatory cytokines and growth factors, enabling immune and inflammatory cells to perceive the intracellular environment of cancer cells even when cancer cells do not express any tumor-specific antigens. For example, in anoxic environment, cancer cells can secrete exosomes containing pro-inflammatory factors to promote the invasion and metastasis of cancer cells. In the complex tumor microenvironment, both tumor cells and various stromal cells will secrete specific exosomes, and promote the development of tumors through various ways, so that tumor cells have drug resistance, and bring adverse effects on the clinical treatment of tumor patients. MicroRNAs and long noncoding RNA as hot keywords play important roles in regulating and mediating tumor development, and their specificity makes them important biomarkers for cancer prediction and diagnosis. Highlighting word analysis shows that microRNAs secreted by leukemia patients can effectively promote the proliferation of malignant cells and the development of cardiovascular diseases. At the same time, exosomes can induce the secretion of some microRNAs in patients, leading to

Extended author information available on the last page of the article

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cardiac repair and regeneration. Therefore, the detection and screening of microRNAs plays a crucial role in predicting the incidence of cardiovascular diseases in patients.

Conclusion Exosomes have attracted increasing attention due to their significant heterogeneity and ability to regulate the tumor immune microenvironment. However, tumor cell-derived exosomes accelerate tumor progression by enhancing immunosuppression and inflammation, increasing oxidative stress, and promoting angiogenesis, which may lead to poor prognosis.

Keywords Exosome · Tumour · Inflammation · Visualization · CiteSpace · VOSviewer

Abbreviations

MVBs	Polyvesicular bodies
miRNA	MicroRNA
IF	Impact factor
JCR	Journal citation reports

Introduction

Exosomes are extracellular vesicles rich in various proteins and nucleic acids (Mathivanan et al. 2010; Simons et al. 2009). All types of cells can secrete exosomes into various body fluids through polyvesicular bodies (MVBs) with plasma membranes and mediate intercellular communication (Gross et al. 2012). Exosomes carry microRNA (miRNA), mRNA, protein and other biology-related substances to complete the transfer and transport between cells (Gross et al. 2012), which is an important medium for intercellular communication (Bang and Thum, 2012). Its important role in the occurrence and development of diseases has aroused attention in the clinical medical community, including cancer (Qiu et al. 2024), neurodegenerative disease (Gao et al. 2021), and inflammatory disease (Console et al. 2019). The study has shown (Yu et al. 2022) that exosomes can be used as a potential biomarker and therapeutic target. Several clinical trials have been conducted to explore the possibility of disease diagnosis, treatment, and monitoring using exosomes, such as the application of exosomes in cardiovascular disease prevention and diagnosis (Zadeh et al. 2020), tumor treatment (Fang et al. 2023), and early cancer diagnosis (Deng et al. 2022).

Inflammation is considered to be a histological response of the body to foreign invasion or damage, which is a basic defense mechanism of the body (Han et al. 2017; Tian et al. 2022). Recent research on tumor suggested (Bi et al. 2022) that inflammation may induce early tumorigenesis, and early tumor can also induce tumor immunity. Proinflammatory carcinogenesis may be the result of environmental changes and multiple cell interactions (Niu et al. 2023), such as increased genomic instability (Salmaninejad et al. 2021), abnormal cell proliferation (Zhang et al. 2021), changes in the stromal environment (Niu et al. 2023), and transitions between epithelial and mesenchymal states (Liu et al. 2015). Inflammatory factors can activate inflammation-related transcription factors, leading to the activation of pro-tumor signaling pathways, so inflammation can induce tumorigenesis (De Silva et al. 2018; Lu et al. 2006).

Exosomes also play a driving role in the process of proinflammatory carcinogenesis. Various substances contained in exosomes such as miRNAs (miRs), cytokines, chemokines, and clotting factors (Vlassov et al. 2012). Exosomes can cause immune system dysfunction and damage to vascular endothelial cells through their clotting activity and release of cytokines and chemokines (Zadeh et al. 2020). At the same time, Due to the protective of exosomes, functional RNAs such as mRNA and miRNA present in exosomes of the blood circulation can avoid rapid degradation and maintain stability compared with free RNAs (Colombo et al. 2014; Ge et al. 2014), and play the function of long-distance signal transmission and provide conditions for distant tumor metastasis (Tsui et al. 2002). Therefore, these exosomes promote the occurrence and development of both malignant tumors and cardiovascular diseases (Zadeh et al. 2020; Yue et al. 2020). The tumor-derived exosomes can induce changes in immune cell function by stimulating bone marrow cells to produce inflammatory mediators or by direct delivery to target cells via these extracellular vesicles (Rupp et al. 2011). The direction of this functional change (stimulation or inhibition) seems to depend on the duration of the interaction between cells and exosomes, i.e. the length of time exposed to inflammatory factors (Altevogt et al. 2014). The key factors in this process are the number of exosomes and the presence of soluble immunosuppressive factors in the tumor microenvironment (Peng et al. 2023). Meanwhile, tumor, exosomes and inflammation are regulated through complex delivery and signaling pathways, which affect the occurrence and development of tumors.

Citation space software (Cite Space) is an information visualization software based on JAVA language and citation analysis theory jointly developed by Dr. Chaomei Chen of Drexel University and WISE Laboratory of Dalian University of Technology (Chen et al. 2019). The structure, rule and distribution of scientific knowledge are presented as a "scientific knowledge map" through visualization. On

the one hand, the development of visualization came from Thomas Kuhn's conception of scientific structure, which provides the philosophical basis for Cite Space to find out the rise and fall of paradigms from scientific literature. On the other hand, it came from the conception of structural hole theory, which promotes the birth of various network cooperative maps and the development of citation networks (Shneider et al. 2009).

Bibliometric analysis software VOS viewer is a Java-based free software developed by van Eck and Waltman of Science and Technology Research Center of Leiden University in the Netherlands in 2009. It is mainly oriented to literature data, adapted to the analysis of a unidirectional network, and focuses on the visualization of scientific knowledge (van Eck et al. 2010).

Both bibliometric analysis and visualization enable co-citations and cluster analysis of authors, journals, institutions, and keywords. However, the data standardization algorithms and visual presentation methods are different, and Cite Space has advantages in revealing the dynamic development patterns of disciplines and discovering the research hotspots based on time series (Börner et al. 2012). The VOS viewer software is preferred when there is a large amount of node data or data clarity required (Skupin et al. 2004).

Therefore, in this study, visualization and bibliometric analysis were combined to summarize and analyze the global research literature on tumor-derived exosomes and inflammatory response, and to discuss the latest development trend, frontier hot spots and future research trends in this field, providing new ideas for clinical diagnosis and treatment of tumors.

Materials and methods

Inclusion and exclusion criteria of data collection

The Mesh search term is used to find synonyms of keywords, and the search formula is set as: "TS = (Exosomes OR Exosome*) AND TS = (Inflammations OR Inflammation* OR Innate Inflammatory Response OR Inflammatory Response, Innate OR Innate Inflammatory Responses) AND TS = (Neoplasms OR Neoplasm* OR Tumor OR Neoplasm OR Tumors OR Neoplasia OR Neoplasias OR Cancer OR Cancers OR Malignant Neoplasm OR Malignancy OR Malignancies OR Malignant Neoplasms OR Neoplasm, Malignant OR Neoplasms, Malignant OR Benign Neoplasms OR Benign Neoplasm OR Neoplasms, Benign OR Neoplasm, Benign)".

Articles published in English from January 1, 2005 to January 31, 2024 were searched, and "Article," "Review article," and "Published Online" as article types were selected. Excluding "Book chapters", "Editorial materials", "Proceeding paper", "Meeting abstract" and "Retracted publication", and total 703 articles were obtained before January 31, 2024 to avoid potential bias from subsequent database updates.

Data collection

English literatures were exported in text and recorded contents with "all recorded and cited references". The above articles were imported into CiteSpace6.2.R6 and VOSviewer1.6.20 software respectively. The time nodes in the literature analysis were selected from January 2005 to January 31, 2024.

The node type is set to country, institution, author, keyword, reference, and cited author according to the analysis object, and the rest are default options. The excel spreadsheet was used to collect the following data as bibliometric indicators: total number of publications, year, author, country, journal, and most cited publications.

Observation indicators

The visualization map is generated using Cite Space software, and then the number and size of nodes in the formed map, the color of the outer ring of nodes, and the number of connections were compared to identify the importance and degree of correlation of each node. The higher the centrality of a node, the greater the probability that the node co-appears with other nodes in the literature, and the greater its influence in the co-occurrence network. The important information is summarized for qualitative and quantitative analysis according to above principles and data.

There are three visualization methods for the graphs generated by VOS viewer software, which are network visualization, overlay visualization and density visualization. The visualization analysis based on color changes: the color of the project in network visualization depends on the cluster to which the project belongs; The color of the item in the overlay visualization is determined by the score of the item, and the blue, green and yellow are enhanced successively; Each point in the density visualization has a color that indicates the density of the item at that point, ranging from blue to green to yellow.

Results

Annual publications

The number of published articles can indicate the research degree and development profile of the research field to a certain extent. The number of articles published between January 1, 2005 and January 31, 2024 and their corresponding

citation trends are shown in Fig. 1. As can be seen from Fig. 1, the number of published papers from 2005 to 2015 was relatively small and the growth rate was slow, which was due to the lack of research on exosomes and the unclear related mechanisms. Since 2016, the number of published papers has increased significantly. Thery C published three reviews on exosomes in 2016, which had breakthrough significance in the research on the function and mechanism of exosomes. Since then, authors from more and more countries have participated in the study of exosomes, resulting in a dramatic increase in the number of published papers, and in 2021, the number of published papers reached the peak of the past 20 years.

In general, the number of papers related to tumor-derived exosomes and inflammatory response showed a trend of fluctuating growth and rapid growth, indicating a good development trend in this field. Based on the fitting curve of R2 = 0.9246 (y = 1.4169e0.335x), it is predicted that publication output will show potential growth in 2024, and will also show sustained levels of growth in the future.

Collaboration of authors from different countries

Based on the articles collected, authors from 61 countries studied tumor-derived exosomes and inflammatory responses, most of which were concentrated in the Northern Hemisphere. In addition, author collaboration links between countries and regions are also mainly located in the Northern Hemisphere. For the southern Hemisphere, Australian scholars have more prominent research results and contributions in this field, and maintain a high frequency of contact with researchers in other countries.

The top ten countries or regions with the largest number of published papers in this field are shown in Table 1. A total of seven countries have centrality greater than 0.1, namely China, the United States, Italy, Germany, Iran, the United Kingdom and the Netherlands. The country with the highest number of publications is China (285, 40.54%), and the second place is the United States (171, 24.32%), China and the United States as the two countries with the most publications, together accounting for more than half of the total, which indicates that they have a significant influence in this field.

The United States has formed cooperation networks or cooperation belts with dozens of countries in this field. China has a prominent advantage in the number of published papers, but the degree of cooperation and node centrality with other countries are relatively less (see Fig. 2).

Table 1 Top 10 countries with the highest number of publications

Ranking	Country	Count (%)	Centrality	First year
1	China	285 (40.54)	0.17	2008
2	USA	171 (24.32)	0.56	2007
3	Italy	43 (6.12)	0.12	2010
4	Germany	41 (5.83)	0.14	2012
5	Japan	35 (4.98)	0.07	2013
6	Korea	30 (4.27)	0.02	2014
7	Iran	27 (3.84)	0.15	2016
8	England	26 (3.70)	0.31	2012
9	Spain	21 (2.99)	0.02	2015
10	Netherlands	18 (2.56)	0.11	2012

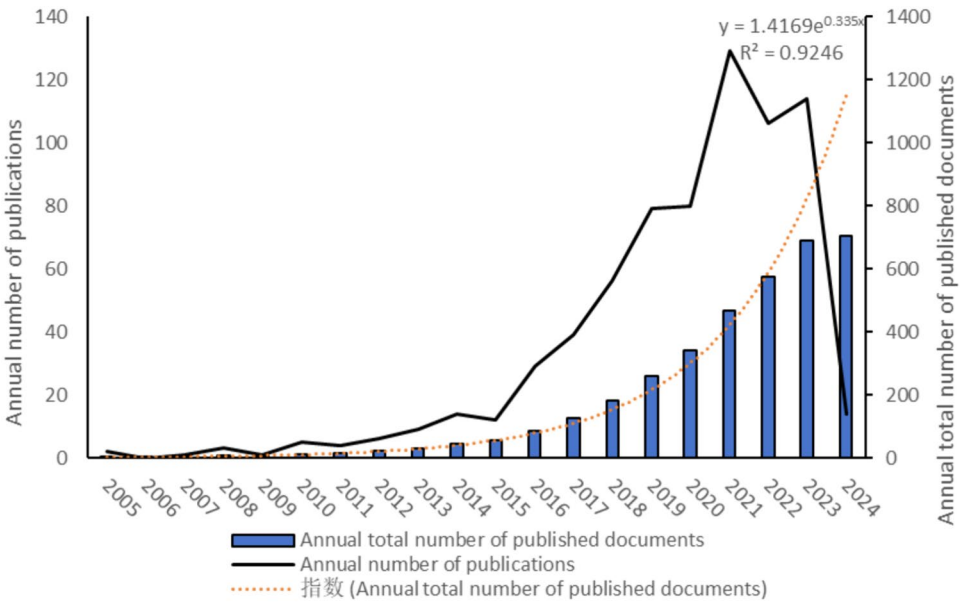

Fig. 1 2005–2024 Trend chart of publication

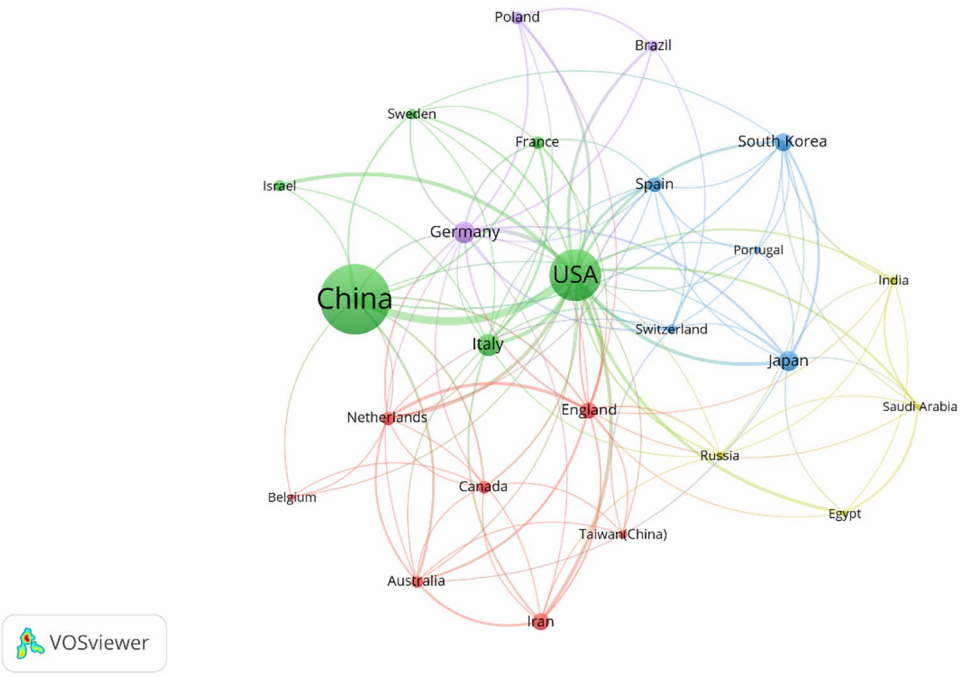

Fig. 2 Country cooperation chart

The agency of author affiliation

The 703 articles on tumor exosomes associated with inflammatory responses came from 305 institutions. The top 11 institutions were ranked according to the number of published articles (Table 2), among which the institution with the largest number of published articles was Shanghai Jiao Tong University, with 19 articles, followed by PCSHE, with 16 articles.

The cooperation among institutions is shown in Fig. 3. In all partnerships, the denser the lines of the cooperation network, the more extensive the cooperation between institutions. Due to geographical location and other factors, the more opportunities for institutional cooperation in the same country, the closer the contact, showing that institutional cooperation has a significant regional. Shanghai Jiao Tong University and Fudan University have gradually formed a larger cooperative network center, and PCSHE has worked closely with the State University System of Florida. Among them, the number of papers published by Chinese institutions is high, and the cooperation network of American institutions is close, which has promoted the development of this field.

Published journal analysis

Between January 2005 and January 2024, studies on tumor-derived exosomes and inflammatory responses were

Table 2 The top 11 institutions in the number of publications

Ranking	Institution	Country	Count	Centrality	Proportion
1	Shanghai Jiao Tong University	China	19	0.02	2.7
2	Pennsylvania Commonwealth System of Higher Education (PCSHE)	USA	16	0.11	2.3
3	Helmholtz Association	Germany	12	0.16	1.7
4	Nanjing Medical University	China	12	0.07	1.7
5	Zhengzhou University	China	11	0.04	1.6
6	Harvard University	USA	11	0.15	1.6
7	Chinese Academy of Medical Sciences-Peking Union Medical College	China	11	0.01	1.6
8	Chinese Academy of Sciences	China	10	0.06	1.4
9	University of California System	USA	10	0.08	1.4
10	Tehran University of Medical Sciences	Iran	10	0.03	1.4
11	Zhejiang University	China	10	0.02	1.4

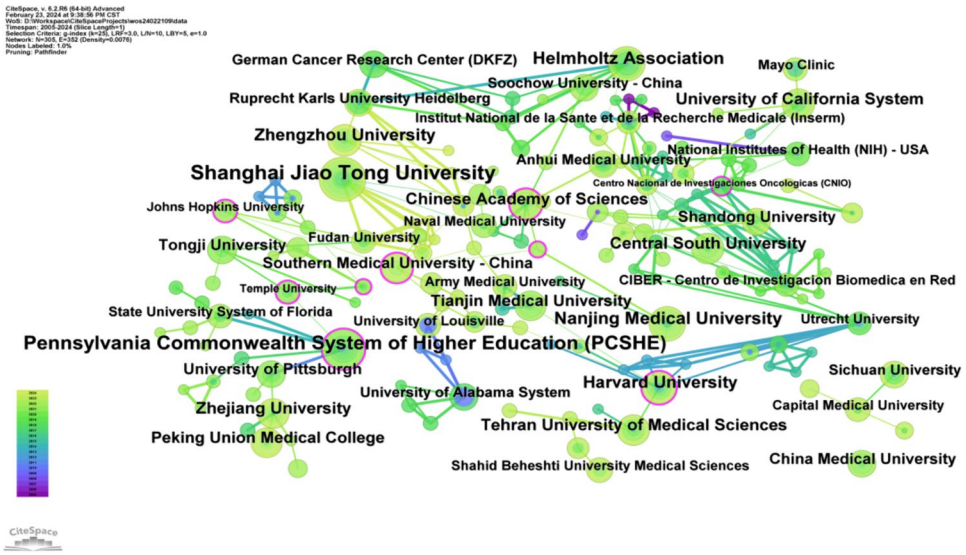

Fig. 3 The collaborative network of the authors' institutions

published in 60 journals worldwide, and Table 3 lists the top 10 journals in number of articles published. Front immunol was the most published journal (n = 5.83%) with an impact factor of 7.3. Among the top 10 journals are five Q1 journals and five Q2 journals. Among the top 10 most cited journals, Q1 accounted for 6 and Q2 accounted for 4, indicating that these journals have a high influence and evaluation in this field, indirectly reflecting that the research results in this field have a greater contribution, the overall research level is high. The influence of a journal is largely determined by the number of citations it receives, as the number of citations reflects the extent to which its articles are cited and used by scholars and researchers in the field. Of the 10 most-cited journals, PLOS ONE was cited the most frequently (1158 times).

The cluster analysis results of journals and co-cited journals are shown in Figs. 4 and 5. VOS viewer software can be used to directly observe the collaboration network among journals and its detailed cooperation status. Journals are divided into four categories according to their co-citation frequency, and articles in the same type of journals may have similar research directions and internal logic.

The double mapping superposition diagram of the journal study is shown in Fig. 6. The prominent yellow in the diagram is the citation path. The left side represents the type of journal cited, the right side represents the type of journal published in the article, the English on the figure is the research field represented by these journals, and the left side represent articles published in journals related to molecular, biological, immunological research that are cited in journal articles related to molecular, biological, genetic research. Relevant studies have laid a foundation for the study of the relationship between tumor-derived exosomes and inflammatory response.

Table 3 The top 10 journals and cited journals

Rank	Count	Co-cited journal	IF (2023)	JCR	Co-cited journal	IF (2023)	JCR
1	41	FRONT IMMUNOL	7.3	Q1	PLOS ONE	3.7	Q2
2	30	INT J MOL SCI	5.6	Q1	J IMMUNOL	4.4	Q2
3	16	CANCERS	5.2	Q2	CANCER RES	11.2	Q1
4	13	CELLS-BASEL	6.0	Q2	P NATL ACAD SCI USA	11.1	Q1
5	12	SCI REP-UK	4.6	Q2	J BIOL CHEM	4.8	Q2
6	11	FRONTIERS IN CELL AND DEVELOPMENTAL BIOLOGY	5.5	Q2	SCI REP-UK	4.6	Q2
7	10	JOURNAL OF EXTRACELLULAR VESICLES	0.1	Q1	BLOOD	20.3	Q1
8	10	STEM CELL RES THER	7.5	Q1	JOURNAL OF EXTRACELLULAR VESICLES	0.1	Q1
9	8	BIOMEDICINES	4.7	Q2	FRONT IMMUNOL	7.3	Q1
10	8	CELL DEATH DIS	9.0	Q1	NATURE	64.8	Q1

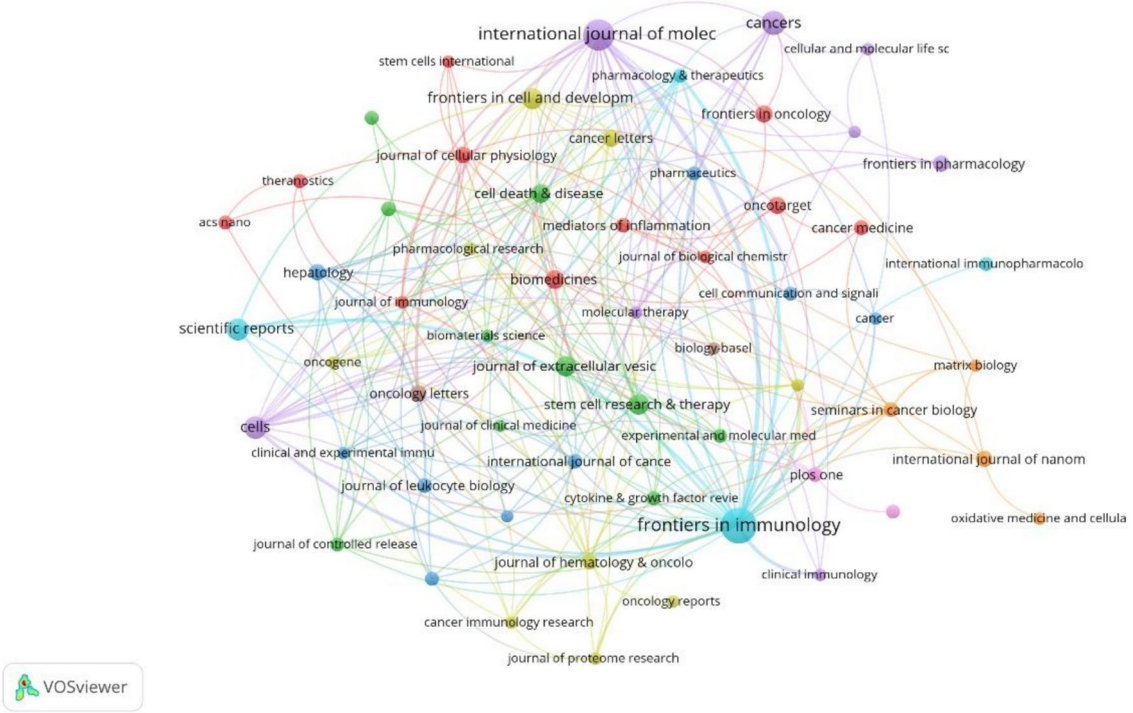

Fig. 4 Clustering analysis of periodicals

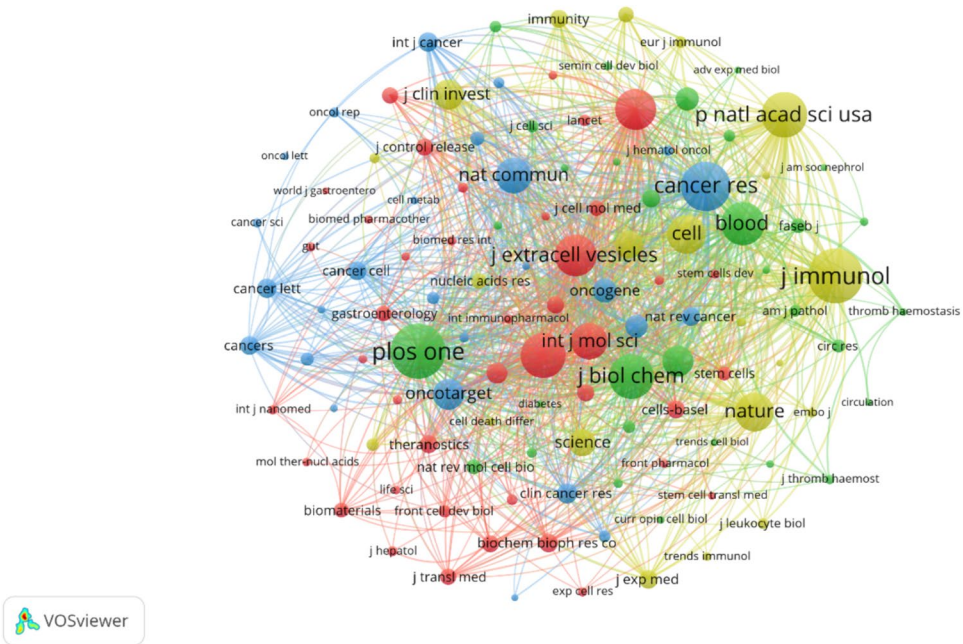

Fig. 5 Cluster analysis of co-cited journals

Author analysise

There were 448 authors in the selected articles. The top 11 authors ranked according to the number of published articles and frequency of citations, which are shown in Table 4. The results show that the teams of Zhang, Hoong-ge, Grizzle, William, and the teams of Kwon, Yoojung, Kim, Youngmi have produced more articles and made outstanding research contributions.

As shown in Fig. 7, a total of 14 author cooperation networks have been formed in this field, and the 11 authors

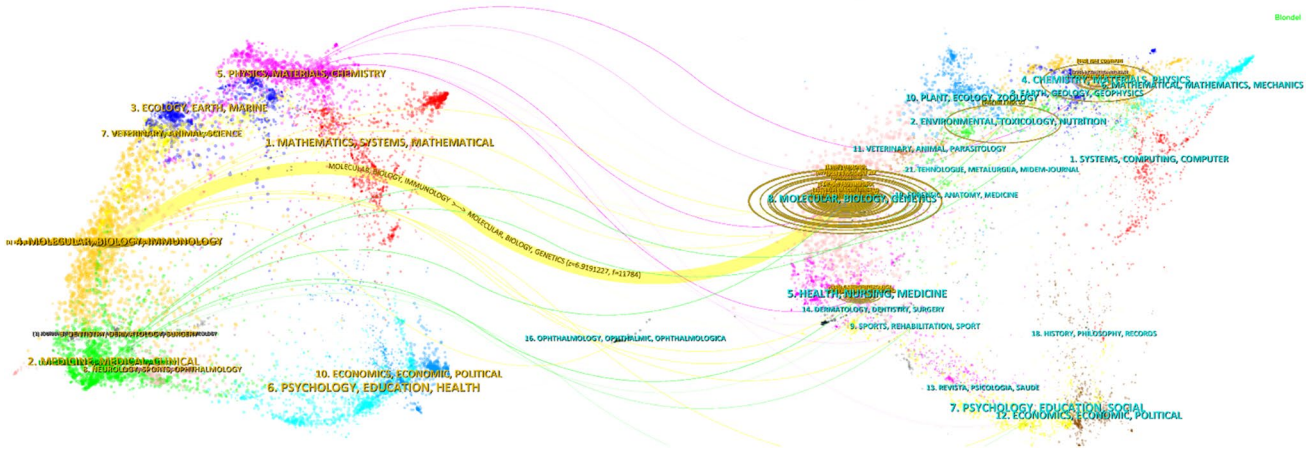

Fig. 6 Double mapping overlay of journal research

Table 4 The 11 authors with the largest number of publications

Ranking	Author	Country	Institution	Count
1	Zhang, Huang-Ge	USA	Univ Louisville, Brown Canc Ctr	5
2	Xiang, Xiaoyu	USA	Univ Louisville, Brown Canc Ctr	5
3	Grizzle, William	USA	Department of Pathology, University of Alabama at Birmingham	4
4	Zhuang, Xiaoying	USA	Univ Louisville, Brown Canc Ctr	4
5	Liu, Yuelong	USA	Department of Medicine, University of Alabama at Birmingham	4
6	Kim, Misun	Korea	Department of Biochemistry, Kangwon National University	4
7	Jeoung, Dooil	Korea	Department of Biochemistry, College of Natural Sciences, Kangwon National University	4
8	Kim, Youngmi	Korea	Department of Biochemistry, Kangwon National University	4
9	Kwon, Yoojung	Korea	Department of Biochemistry, Kangwon National University	4
10	Jung, Hyun Suk	Korea	Department of Biochemistry, Kangwon National University	4
11	Yang, Yang	China	School of Public Health, Shanghai Jiao Tong University School of Medicine	4

with the highest number of publications are all in the above two teams.

The article citation frequency is sorted. The 10 authors with the most citation frequency is shown in Table 5. Among them, the article by THERY C from France has been cited 202 times and has the highest citation frequency. As the main researcher on the basic function of exosomes, THERY C established the gold standard for extraction, separation and identification of exosomes-the ultra-fast centrifuge method (Tkach et al. 2017). It was confirmed that miRNA can be transported into target cells by entering small EVs, and play a role in directly regulating miRNA targets and helping virus spread, which indicates that exosomes promote tumor spread and metastasis. It was found that all EVs could activate *T* cells, but small vesicles and medium vesicles were induced into Th1 type, while large vesicles were induced into Th2 type. This difference was due to the surface of large vesicles being rich in CD40, while the surface of small vesicles and medium vesicles being rich in CD80 (Tkach et al. 2017; Tkach et al. 2016). On this basis, the comparison between tumor-derived exosomes and immune-cell-derived exosomes showed that 100 k precipitate products in tumor cells were very different from 100 k precipitate products in DC cells, and the effect of malignant tumor cell-derived EV on immune cell secretion of inflammatory factors was also different, the stimulating effect of exosomes is the most obvious (Fan et al. 2018). This is because the contents of tumor exosomes and immune exosomes are different and specific, and the tumor-derived exosomes have a prominent stimulating effect on the secretion of inflammatory factors. These differences and characteristics are inevitably related to the physical basis of exosomes such as size and contents. THERY C's research is closely related to the study of tumor-derived exosomes and inflammatory responses, which has promoted the development of this field.

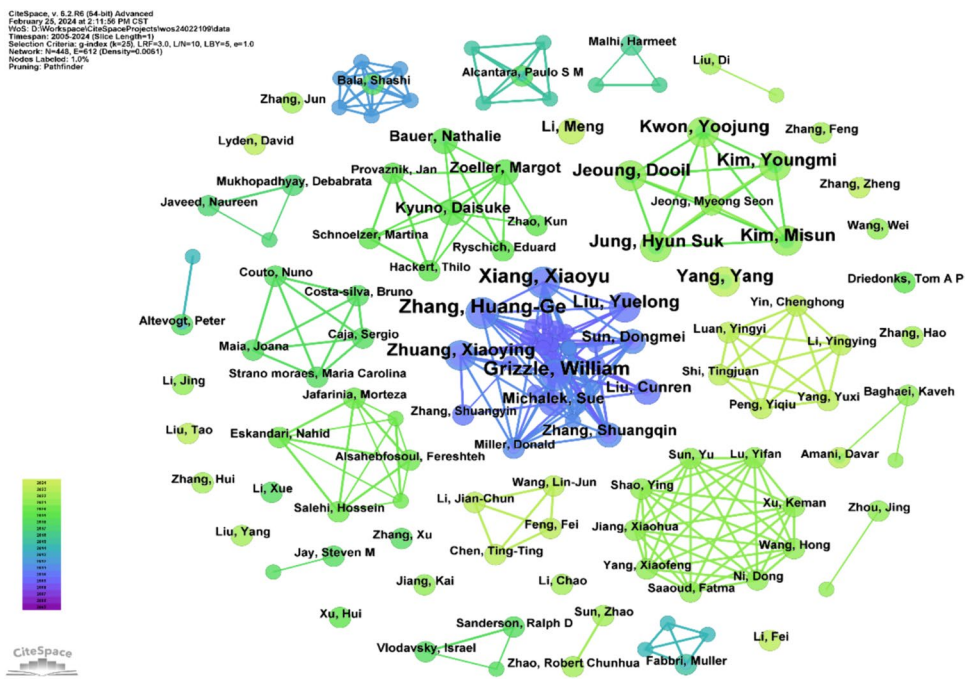

Fig. 7 Author cooperation network diagram

Table 5 The 10 authors whose articles are cited most frequently

Ranking	Author	Country	Frequency	Half life
1	THÉRY C	France	202	14.5
2	VALADI H	Sweden	135	6.5
3	RAPOSO G	Netherlands	127	12.5
4	KALLURI R	USA	108	3.5
5	COLOMBO M	France	101	3.5
6	VAN NIELG	France	87	3.5
7	ZHANG Y	USA	87	6.5
8	PEINADO H	USA	79	5.5
9	HOSHINO A	USA	67	4.5
10	KOWAL J	France	65	3.5

The cited frequency of the selected articles

The cited frequency of the 703 included papers was ranked, among which the top 11 cited articles were listed in Table 6. Among the 11 articles, 9 were related to the basic function of exosomes, 1 was about exosomal immunosuppression, and 1 was about tumor-derived exosomes. The title "Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines" was cited 84 times, which is the highest cited frequency. Under the leadership of Thery C, this paper systematically summarizes the exosome research in the past 10 years, including naming principles, isolation and extraction techniques, evolution characterization of EVs, and biological activities, which provide convenience and guidance for subsequent researchers. Also cited as a high-frequency article "The biology, function, and biomedical applications of exosomes" introduced the biogenetic mechanism of exosomes in detail: double invagination of plasma membrane and formation of intracellular polyvesicles (MVB) containing intracellular vesicles (ILV). Exosome heterogeneity: The heterogeneity of exosomes reflects their size, content, functional effects on recipient cells, and cell origin. Intercellular communication: the proteome in exosomes mirrors the proteome of the original cell, exosome proteins from cancer cells, which can selectively induce specific signals in recipient cells to regulate processes such as development, immune response, and disease when exosome proteins from cancer cells undergo carcinogenic changes and secreted into exosomes again.

Figure 8 shows the cited article with outburst. As the citation with the strongest outburst (intensity = 21.47) in the relevant studies, and the above mentioned articles has the outbreak duration since 2020, which reflects the significance of this article in the study on the correlation between tumour-derived exosomes and inflammatory response.

Keywords co-occurrence

Keywords represent the central theme of a paper, and keyword co-occurrence analysis can quickly capture the research hotspots in a certain field. The keywords were summarized using VOSviewer as shown in Fig. 9. Keywords are displayed in a larger font, and the larger the nodes in the graph, the more frequently they appear; The darker the color, the higher the frequency. According to the node size

Table 6 The 11 most frequently cited papers

Ranking	The first author	Cited reference	Frequency	Centrality	Year
1	Théry C	Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines	84	0.03	2018
2	Kalluri R	The biology, function, and biomedical applications of exosomes	72	0.01	2020
3	van Niel G	Shedding light on the cell biology of extracellular vesicles	62	0.04	2018
4	Mathieu M	Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication	45	0.09	2019
5	Chen G	Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response	33	0.08	2018
6	Raposo G	Extracellular vesicles: exosomes, microvesicles, and friends	33	0.2	2013
7	Hoshino A	Tumour exosome integrins determine organotropic metastasis	31	0.13	2015
8	Colombo M	Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles	31	0.07	2014
9	Kowal J	Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes	28	0.1	2016
10	Hessvik NP	Current knowledge on exosome biogenesis and release	27	0.01	2018
11	Tkach M	Communication by Extracellular Vesicles: Where We Are and Where We Need to Go	27	0.1	2016

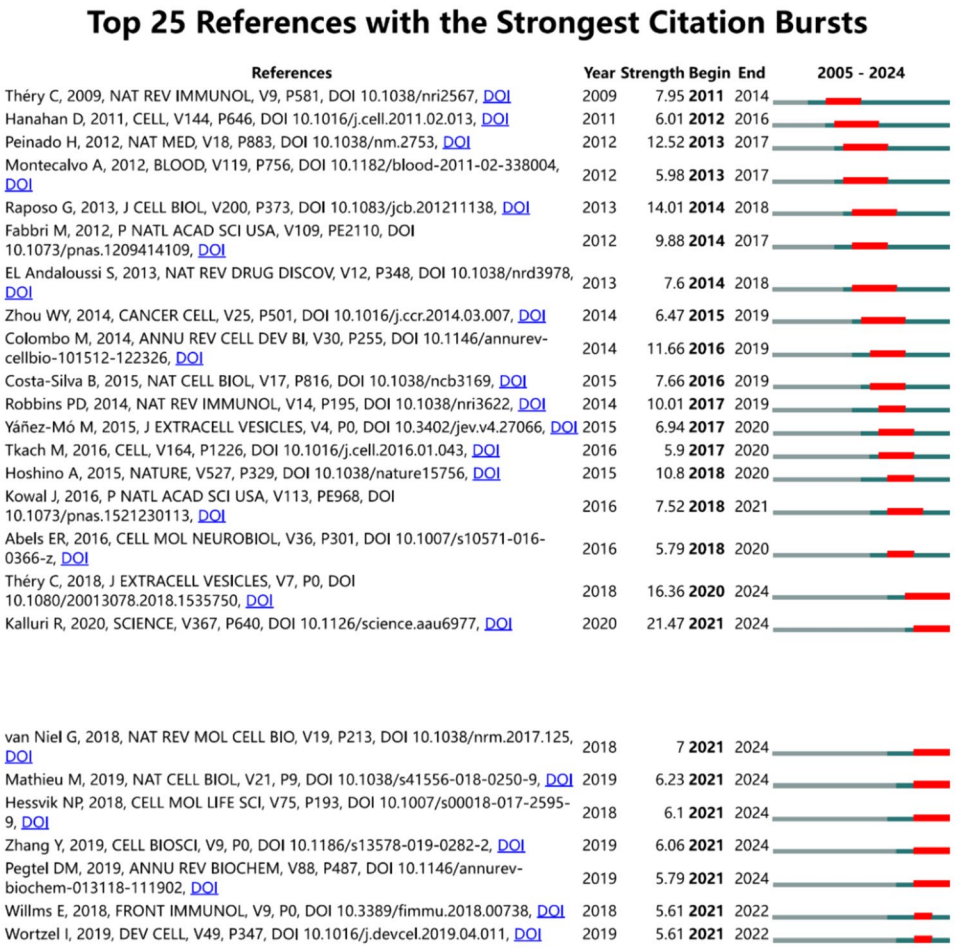

Fig. 8 Top 25 references with the strongest citation bursts

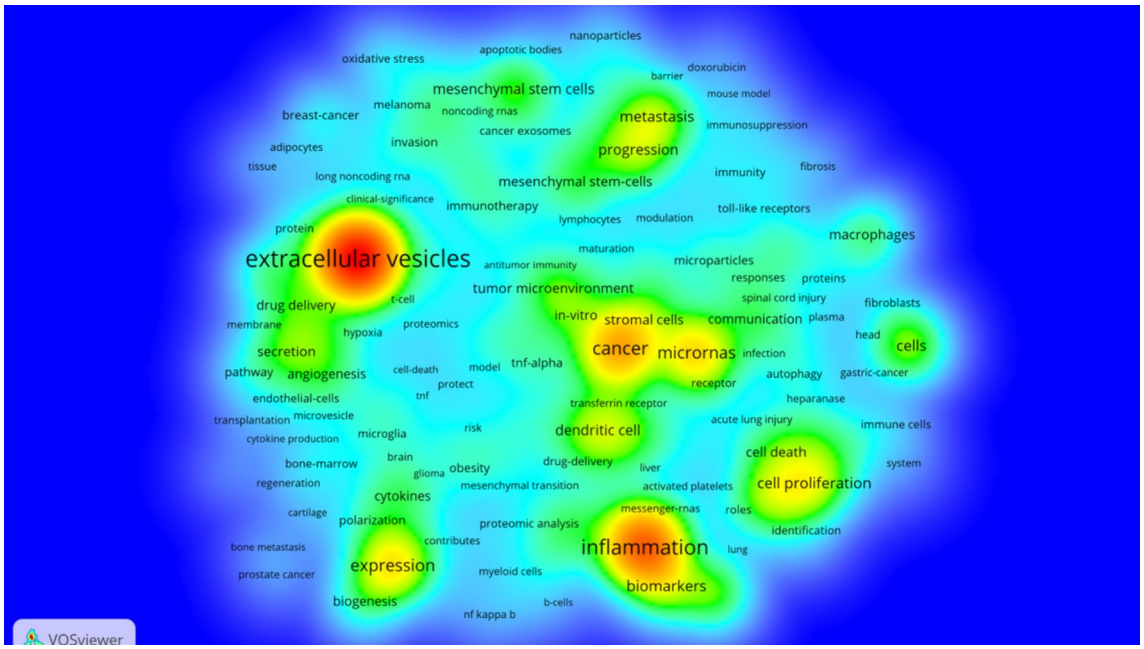

Fig. 9 Keyword density map

and color depth, it can be intuitively seen that extracellular vesicles (378), inflammation (218), cancer (142), expression (137), mesenchymal stem cells (133), Micrornas (99) and **etc.** are highly researched heat in this field.

The average publication year of each keyword is analyzed in Fig. 10. The changes from blue to yellow in the figure represent the passage of time, which also indicates that the use of keywords develops with the passage of time. Immunity is the earliest keyword, which is closely related to the development history of exosomes, followed by extracellular vesicles and inflammation. In recent years, the development of obesity, expression, mesenchymal stem cells, microRNAs and etc. high-frequency keywords are basically concentrated in 2019–2020.

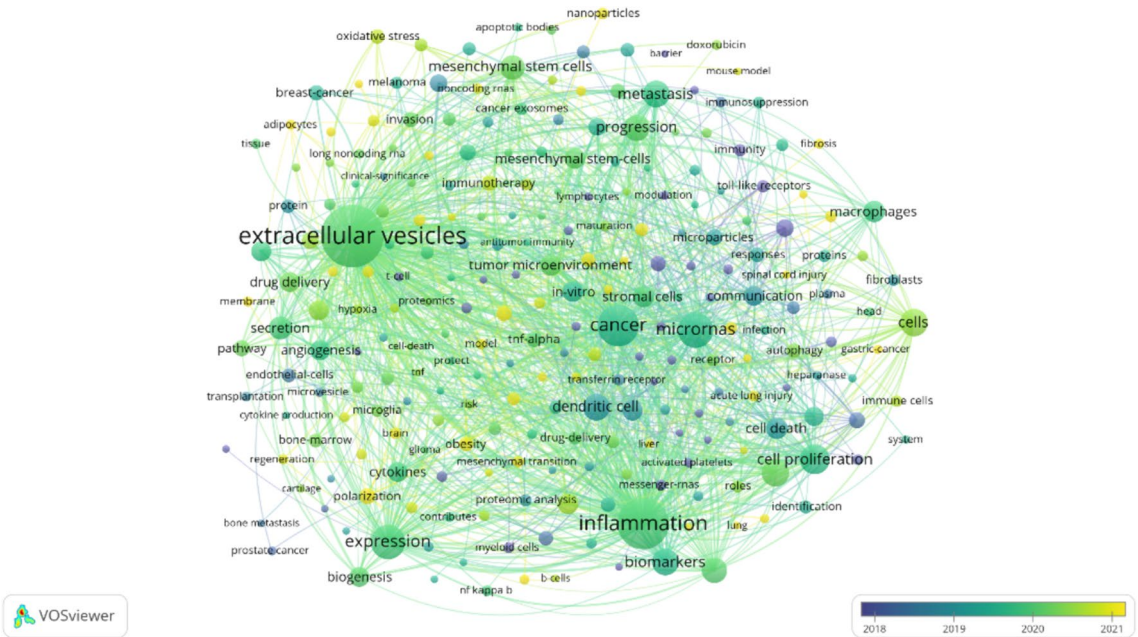

Fig. 10 Keyword overlay diagram

The above results indicate that the direction of research in this field has changed with the passage of time. From basic research to integration with inflammation and tumor. This process promotes the development of related fields and points the way for future development from basic research to integration with inflammation and cancer.

Keywords cluster

Cluster analysis is a statistical analysis technique that divides research objects into relatively homogeneous groups, which can intuitively understand the general research direction of the analyzed field or discipline.

A total of 9 clusters are generated by the keyword cluster analysis, as shown in Fig. 11, which include #0 drug delivery, #1 progression, #2 gastric cancer, #3 circulating endothelial microparticles, #4 T cells, #5 long noncoding RNA, #6 adipose tissue, #7 extracellular vesicles, #8 tumor microenvironment. These clusters cover three fields respectively. Cluster #0, #3, #5, and #7 are related to exosomes, cluster #1, #2, and #8 are related to tumors, and cluster #4 is related to immunity. In fact, the identification of these keywords and clusters helps to reveal current research hotspots and frontiers, and provide references for future research in this field.

Each cluster keyword reflects the research progress and trend in this field according to the change of time, which are shown in Fig. 12. It can be seen from the figure that there were few studies on exosomes, and more exploration on extracellular vesicles and progression from January 2005 to December 2015.

Since January 2016, the research on exosomes has been widely distributed in various fields. In particular, the research on exosomes and drug delivery, cancer treatment, and immunity have pushed to a new high after THERY C revealed the intercellular communication of extracellular vesicles in October 2016, and the exploration of exosomes from various fields and angles has laid a foundation for the study of clinical related diseases.

Emergent word analysis

Emergent word analysis can detect the words with high frequency change rate from a large number of subject words in a certain period of time, and can be used to highlight the most active research areas in a specific field. It indicates that the research related to the keyword may be at the forefront of research if a keyword is still in the research explosion period in recent years. Figure 13 shows the top 22 keywords with the highest burst intensity. Among them, the prominent word "MicroRNAs" has been hot for 5 years since 2012, and its popularity continues to soar due to its dual role in the diagnosis and treatment of cardiovascular diseases. On the one hand, microRNAs secreted by leukemia patients can effectively promote the proliferation of malignant cells and the development of cardiovascular diseases (Chinese Society of Hematology et al. 2019); On the other hand, exosomes can induce the secretion of

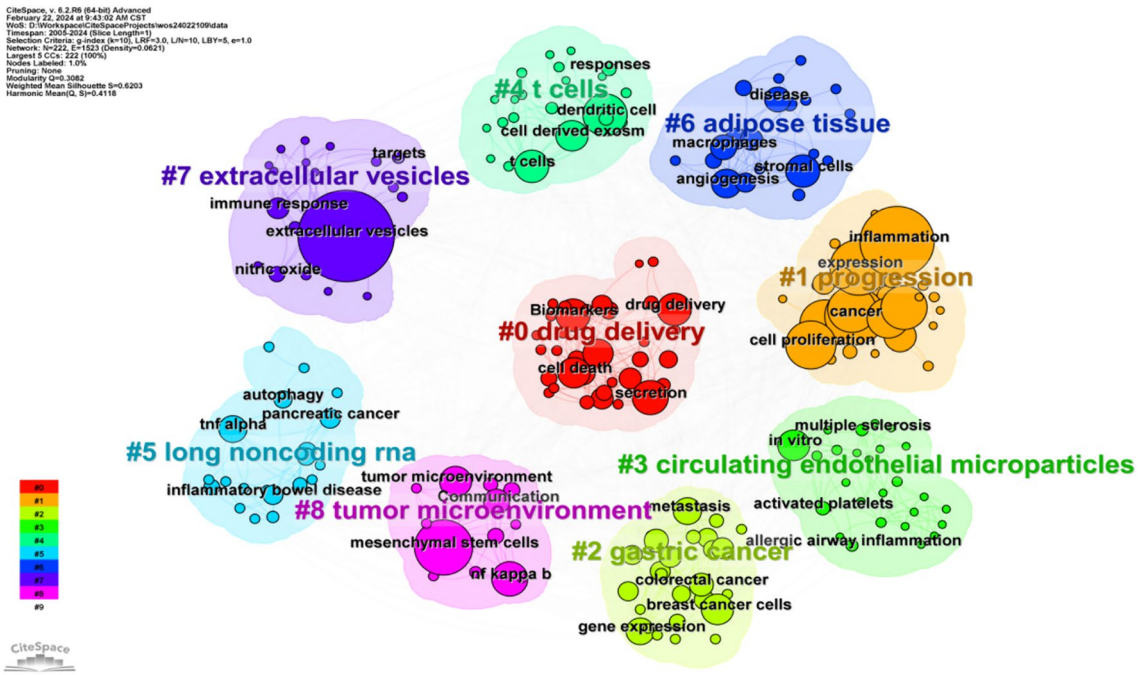

Fig. 11 Keyword clustering diagram

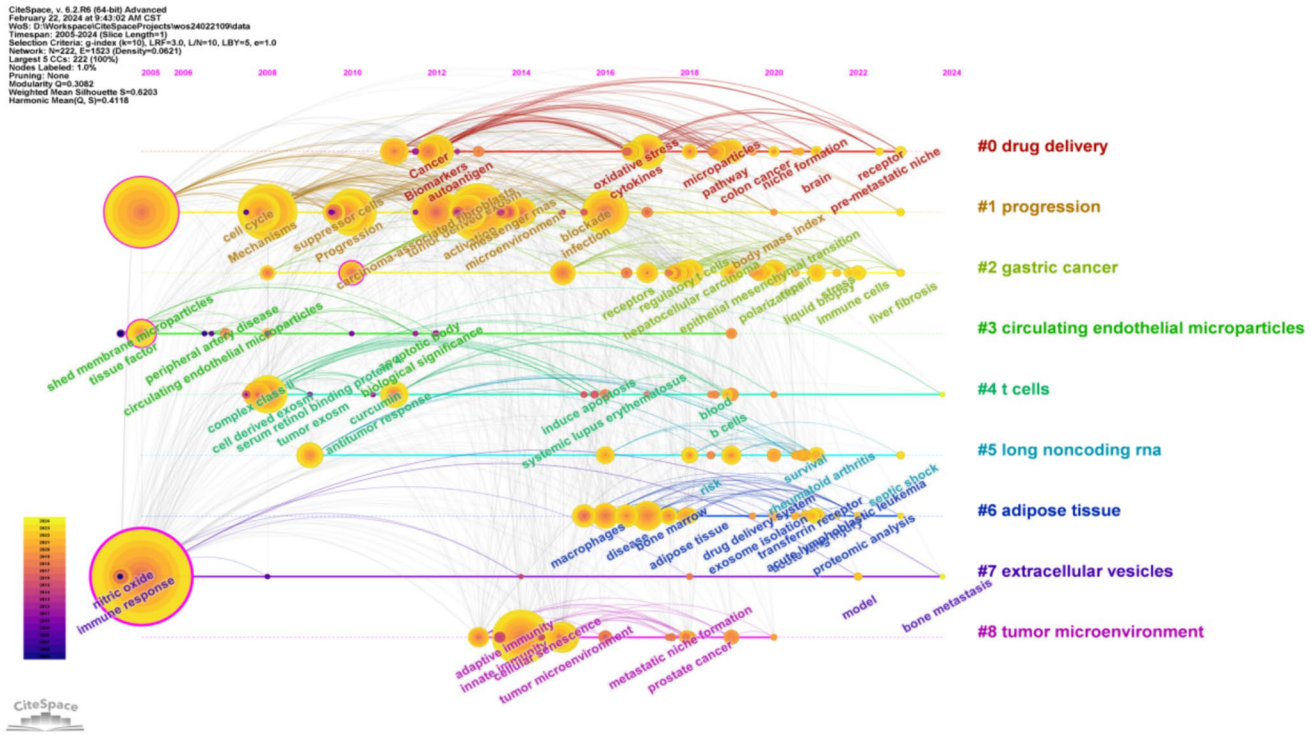

Fig. 12 Keyword clustering time diagram

Keywords	Year	Strength	Begin	End	2005 - 2024
activated platelets	2008	2.51	2008	2012	
suppressor cells	2010	3.2	2010	2019	
horizontal transfer	2010	2.6	2010	2013	
gene-expression	2010	2.54	2010	2018	
myeloid cells	2010	2.46	2010	2016	
t-cells	2011	2.8	2011	2016	
Micrornas	2012	3.76	2012	2017	
membrane-vesicles	2013	4.93	2013	2016	
tumor derived exosm	2013	3.3	2013	2018	
innate immunity	2014	2.65	2014	2015	
nf kappa b	2015	2.76	2015	2016	
regulatory t cells	2016	3.28	2016	2018	
responses	2016	2.95	2016	2020	
macrophages	2016	2.82	2016	2017	
Cancer	2014	2.65	2017	2019	
Melanoma	2018	3.1	2018	2020	
ovarian cancer	2018	2.86	2018	2019	
toll like receptors	2018	2.33	2018	2020	
mediated transfer	2019	3.27	2019	2020	
roles	2021	2.98	2021	2022	
liquid biopsy	2021	2.77	2021	2022	
obesity	2022	3.15	2022	2024	

Fig. 13 The top 22 keywords with the highest burst intensity

some microRNAs in patients, leading to cardiac repair and regeneration, and their repair and regeneration functions are widely used in ischemia–reperfusion injury (Hematology Oncology Committee et al 2021). For example, scientists have found that human umbilical cord mesenchymal stem cell-derived exosomes promote cardiac repair after ischemic injury by protecting cardiomyocytes from apoptosis and promoting cell proliferation and angiogenesis, but human umbilical cord mesenchymal stem cells without exosomes can hardly improve cardiac function (Zhao et al. 2015; Yu et al. 2015). The reason for this dual nature is that there are many different types of microRNAs, each of them performs similar or very different functions. Therefore, detection and screening of microRNAs plays a crucial role in predicting treatment resistance and cardiovascular disease incidence in patients (Zadeh et al. 2020).

The emergent word "obesity", as the latest emergent word in recent years, is closely related to inflammation, tumor and exosomes. Obesity is a chronic inflammatory disease (Ouchi et al. 2011); It's also a risk factor for breast cancer (Fan et al. 2014). Its mechanism is closely related to miR-140 encapsulated by exosomes derived from adipocytes (Gernapudi et al. 2015). It increases breast cancer cell migration and promotes cancer progression while affecting hypoxia-inducing factor α1 activity and enhance the aggressiveness of breast cancer cells in vitro and in vivo. The clarification of the relationship among exosomes, inflammation and tumor will play an important role in guiding clinical drug use and treatment (La Camera et al. 2021).

Discussion

In this study, 703 literatures from the Web of Science database were visualized by using Citespace6.6.R6 and VOSviewer1.6.20 software to analyze the overall situation and research hotspots related to tumor-derived exosomes and immune response in the past two decades.

Two developmental stages of exosome-related research

The number of papers on the relationship between tumor exosomes and inflammatory response is increasing year by year. The 703 articles on exosomes were published from January 2005 to January 2024. The growth in the number of publications related to research is divided into two phases according to the rate of research development and research progress reflected in the number and trend of papers published each year, and the research concentration. The first period was from January 1, 2005 to December 31, 2015, and the number of published articles in this period grew at a slower rate, although the mechanism of intercellular communication for extracellular vesicles was basically known (van Niel et al. 2022), however, the study of exosomes is still in the stage of exploring the mechanism. The second phase is from January 1, 2016 to January 31, 2024, and this period is growing rapidly, and the research on exosomes is more in-depth and extensive.

Tumor cells and their microenvironment typically produce a large number of immunomodulatory molecules that have a negative (suppressor) or positive (activator) effect on the function of immune cells. Tumor microenvironment (TME) can shift immune response from tumor destructive mode to tumor promoting mode based on its composition (Maia et al. 2018).

The components such as immune cells, soluble mediators (cytokines, chemokines, angiogenesis factors, lymphangiogenesis factors, and growth factors) and cell receptors in TME play key roles in the immune response (Bejarano et al. 2021). The discovery of the communication mechanism of exosomes provides a new idea for the occurrence of tumor immune microenvironment, which is achieved by inhibiting the function of the immune system and preventing uncontrolled inflammation (Othman et al. 2019). For example, exosomes can induce immunosuppression by initiating apoptosis of immune cells (Barros et al. 2018; Keryer-Bibens et al. 2006). The high concentrations of galectin-9 protein are contained in released exosomes of EBV-infected nasopharyngeal cells (Keryer-Bibens et al. 2006; Klibi et al. 2009), which can induce apoptosis of mature Th1 lymphocytes. Another example, colorectal cancer or melanoma cell-derived exosomes help tumors escape from the immune system by triggering the ability to activate FAS-dependent apoptosis of CD8 T cells (Andreola et al. 2002; Ma et al. 2020). A large number of experimental results have gradually confirmed that exosomes are mysterious objects for "cancer immunoediting".

Geographical distribution of authors for selected articles

The authors from China and the United States published the most articles in terms of authors' countries and regions, these publications accounted for more than half of all collected articles. It shows that scholars from these two countries have done more research on this field and played a leading role in the development of this field. The authors of the articles are basically based on the institution, and all the issuing institutions and countries are independent. Therefore, it is necessary to strengthen the cooperation and exchange between research institutions and researchers in various countries, which is conducive to the flow of information, the innovation of research methods, and the rapid development of the field.

Hotspots and frontiers

Keywords are the research theme and core content of the literature, and the use of keyword co-occurrence analysis can help understand the distribution and growth of various research hotspots on a specific topic. The relationship between tumour-derived exosomes and inflammatory response was revealed, and the research hotspots and frontier development status in this field were further determined through using Citespace to conduct co-occurrence map analysis, cluster analysis, outburst word analysis and time zone map analysis for keywords. At the same time, MCA analysis and visual analysis are carried out by using keywords, and the research direction in this field is highlighted by judging the similarity of different keywords.

MiRNA plays an important role in regulating, mediating and predicting tumor

MiRNAs have attracted much attention as a research hotspot and frontier in this field according to keyword co-occurrence, clustering, keyword emergence and age analysis. microRNA is a type of non-coding RNA (ncRNA) rich in exosomes (Cheng et al. 2014). It is also an important carrier and component of exosomes as intercellular material exchange and information exchange (Théry et al. 2011). Its presence reflects the tumor progression, indicates the communication between cells in the tumor microenvironment, and its regulation of tumor cell growth (Chiodoni et al.

2019). The process of gastric cancer can be regarded as a significant case: Tsai and colleagues found that microRNAs participate in the process of gastric cancer induced by Helicobacter pylori infection, revealing that exosomal microRNAs play an important role in the occurrence, development, metastasis, angiogenesis and chemotherapy resistance of gastric cancer (Tsai et al. 2020). Shimoda et al. reported that during the infection of gastric epithelial cells by H. pylori, the expression of mesenchymal epithelial transformation factor (MET) protein activated by exosomes in macrophages was enhanced, which promoted the occurrence and progression of gastric cancer (Shimoda et al. 2016). Another example, miR-140 encapsulated by adipocyte derived exosomes can increase the migration of breast cancer cells and promote cancer progression (Gernapudi et al. 2015). It also induced the activity of hypoxia-inducing factor α1 and enhanced the invasiveness of breast cancer cells in vitro and in vivo (La Camera et al. 2021). Breast cancer cells can secrete miRNA-144 or miRNA-126, which leads to differentiation and remodeling metabolism in beige fat cells, and remodeling fat cells induce tumor proliferation in breast cancer (Wu et al. 2019; Dos Santos et al. 2023). Thus, the interaction between breast cancer and cancer-associated fat cells forms a mutually reinforcing cycle in cancer metastasis.

Limitations

In this study, the articles in the Web of Science database of English core journals were searched using CiteSpace and VOSviewer software, and the 703 literatures were collected, and the research progress of tumor-derived exosomes and inflammatory responses were analyzed in recent years. While these results provide some valuable insights, the study does have some limitations: First, the study lacks other databases or articles published in other languages, so future studies must use databases such as Pubmend or Scopus to expand their coverage; Second, keyword and reference analysis cannot provide enough information to reveal deeper research motivations and specific research processes, and older articles tend to have higher citation rates, while newly published high-quality literature is cited less frequently. Finally, bibliometrics is more suitable for the analysis of macro trends than for the identification of subtle process mechanisms.

Conclusions

This study shows the hot spots and frontiers in the research field related to tumor-derived exosomes and inflammation. The close relationship among tumor, exosome and inflammation are found through articles analysis. Exosomes act as important mediators between tumor and inflammation, which may accelerate tumor progression by enhancing immunosuppression and inflammation, increasing oxidative stress, inhibiting anti-tumor immune response, or promoting angiogenesis. Due to the heterogeneity of exosomes, it provides a new method for clinical diagnosis and treatment. The exploration of extracellular communication mechanisms and pathways of exosomes from different sources will make outstanding contributions to clinical and multi-field research.

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Declarations

Conflicts of interest The authors declare no conflicts of interest regarding the publication of this paper.

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