

Research Trends of Macrophage Polarization: A Bibliometric Analysis

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Abstract

Background: Macrophage polarization is involved in the development of many diseases such as obesity, diabetes, and cancer. This study aimed to understand the trends and hotspots of macrophage polarization research.

Methods: We searched through the Web of Science Core Collection database to obtain original articles in this research domain. CiteSpace, HistCite, and VOSviewer software were used to facilitate the analysis and visualization of scientific productivity and emerging trends.

Results: The survey included 3064 articles, and the annual number of publications exhibited an exponential increase. These articles have received a total of 74,801 citations, and the number of annual citations grew from 68 to 18,074 in a decade. Research on macrophage polarization was performed in 76 countries, and the USA ranked first in terms of research output by contributing 1129 (36.8%) articles. The USA also had the highest H-index, total citations, and highly cited article number. *PLOS One*, *Journal of Immunology*, and *Scientific Reports* were the three journals that published the most articles. Interdisciplinary research areas involving macrophage polarization, such as biomaterials, cancer, and diabetes, were identified by journal citation analysis. The top 20 most productive institutions were located mainly in the USA, France, and China, and top authors originated mainly from the USA and Italy. Tumor biology, obesity, and infection were research hotspots and may be promising in the next few years.

Conclusions: This study provides a comprehensive analysis that delineates the scientific productivity, collaboration, and research hotspots of macrophage polarization research.

Key words: Bibliometric Analysis; Macrophage; Macrophage Polarization

INTRODUCTION

Macrophages are distributed in various kinds of tissue and play an important role in many biological processes such as development, homeostasis, tissue repair, and immune response.^[1,2] Heterogeneity and plasticity are key features of the macrophage lineage.^[3,4] These cells can adapt and respond to microenvironmental stimulation by altering their gene expression profile, metabolism, and function; this phenomenon is called “macrophage polarization.”^[5-7] Macrophages display a continuous spectrum of activation states, the two extremes of which are classically referred to as activated macrophages (CAM or M1) and alternatively activated macrophages (AAM or M2). M1 macrophages can secrete pro-inflammatory factors such as tumor necrosis factor-alpha, nitric oxide, and interleukin (IL)-6. In contrast, M2 macrophages produce anti-inflammatory factors such as transforming growth factor-beta and IL-10.^[8,9] Dysregulated macrophage polarization contributes to many diseases

including obesity,^[10,11] diabetes,^[12,13] atherosclerosis,^[14,15] and cancer.^[16,17] Thousands of articles on macrophage polarization have been published in the 21st century; however, few studies have employed bibliometric analysis of this topic.

Bibliometrics is a useful method to describe the developing trends of a research domain. It can also be used to reveal research hotspots and predict future research foci. The productivity of authors, countries, institutions, and international collaboration can also be evaluated using

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bibliometrics.^[18,19] In recent years, bibliometric analysis has provided insights into many research fields such as drug abuse,^[20,21] cancer,^[22,23] cardiovascular disease,^[24,25] and public health.^[26]

We performed a bibliometric analysis of papers on macrophage polarization published between 2007 and 2016. This work will give a brief overview of the achievements and landmarks in this research domain.

METHODS

Data were obtained from the Science Citation Index Expanded (SCI-E) database of the “Web of Science Core Collection” on October 25, 2017. The search query used was “TS = (macrophage AND polarization).” The timespan was set between the years 2007 and 2016, and the language was set to “English,” and document type was set to “article.” The search resulted in 3064 articles that met the inclusion criteria.

Search results were downloaded and exported into different software applications for further analysis. “Plain Text” was chosen as the file format, and “Full Record and Cited References” was chosen for the record content in order to include all the necessary information.

To assess the information from different aspects, three programs were used to analyze the search results. A total of 76 countries, 753 journals, 17,615 authors, and 2779 institutions were counted using HistCite, a package developed by Eugene Garfield. CiteSpace, developed by Prof. Chaomei Chen, is a tool for information visualization that can help to visualize collaborative networks, document citation networks, and research hotspots,^[27,28] and we used it to analyze the time trends of keywords. VOSviewer is a program run by the Centre for Science and Technology Studies at Leiden University and is a tool for constructing and visualizing bibliometric networks such as co-citation, co-authorship, and term co-occurrence. We used it to present the citation networks of highly cited authors and journals. The visualization of institutional collaboration and MeSH term clustering was also performed with VOSviewer. The 2016 impact factor (IF) of journals was obtained from the Journal Citation Reports on November 1, 2017.

RESULTS

Publication outputs and citation number

There were 3064 articles related to macrophage polarization published between 2007 and 2016. A vast increase in publication number was observed over this period, with annual publications growing from 46 in 2007 to 804 in 2016, with 1962 documents being published between 2014 and 2016 (about 64.0% of the total publications). Publication growth rate varied from 24.2% in 2009 to 56.3% in 2013 [Figure 1a].

These articles have been cited for 75,143 times to date [Figure 1b]. Annual citation number also grew very rapidly,

although the citation number in 2017 was a little lower than that of 2016, since the year 2017 has not yet come to an end at the time of the data collection. The average citation number of these articles was 24.84, and the H-index of the group was 112, indicating that quite a lot of these articles are highly cited.

Contribution of top 10 most productive countries

Seventy-six countries have participated in the publication of macrophage polarization research. Some articles were written by researchers from different countries. The top 10 most productive countries produced 3161 of the total articles. This exceeded the total publication number arising from international collaboration. The USA was the most productive country, with 1129 articles published [Figure 2a], followed by China (618), Germany (296), Japan (264), the United Kingdom (196), Italy (186), France (172), the Netherlands (140), Spain (107), and Canada (97).

There was much variation in the publication growth rates between the different countries. Those of the USA and China were much higher than the others [Figure 2b]. The number of citations is the most commonly used tool to determine the influence of a country in a specified research field. For most countries, the average citation number per paper ranged between 20 and 30, but those of Italy, the United Kingdom, and the USA were much higher. China ranked last with its papers cited 13.91 times on average [Figure 2c].

The H-index of the USA was much higher than the other countries [Figure 2d]. The number of highly cited articles (those cited for over 50 times) was also counted, and US scientists were responsible for 184 highly cited articles, nearly one half of the total [Figure 2e].

Among the most productive countries, the USA frequently participated in international collaboration, and some European countries (France, the United Kingdom, Germany, Italy, etc.) also worked in close collaboration with each another. China worked closely with the USA, whereas Japan scarcely collaborated with other countries [Figure 2f].

Article distribution among journals

The most important journals in a certain research field can be identified by analyzing article distribution, and researchers can use these findings to decide to which journal they should submit their work.

Bradford’s law states that if journals in a field are sequenced according to publication output and divided into three groups, with each group containing the same number of articles, the number of journals in each group will be in the proportions of 1:n:n²; this was used to describe the distribution of articles in this study.

The 3064 retrieved articles were published in 753 SCI-E indexed journals. The top 21 most productive journals published 1016 articles from 2007 to 2016, about one-third of the total publications. According to Bradford’s law, we define these as “core journals” in macrophage polarization

research [Table 1]. *PLOS One*, *Journal of Immunology*, and *Scientific Reports* were the top three journals with the highest numbers of published papers.

Different journals usually favor publication on different scientific subjects, so a regression analysis was conducted between their IFs and the average number of citations per paper. A strong correlation was found between the two variables, yet 3 points representing the journals *Blood*, *Journal of Clinical Investigations*, and *Oncology* deviated much further from the regression line than the others [Figure 3a]. Further analysis revealed that two articles published in *Journal of Clinical Investigations* have been cited 1716 and 1407 times, respectively, pushing up the average citation count substantially. The

average citation count did not match the high IFs of *Blood* and *Oncology*, and the reason for this is unknown.

We defined a “highly cited journal” as one whose total citation number was higher than 100, and, by this criterion, 122 out of the 753 identified journals were highly cited. VOSviewer software was used to analyze the citation network among these [Figure 3b]. In this figure, journals were represented by dots and the dot size is proportional to each journal’s citation number. The journals were divided into seven clusters according to the citation network between them, and the clusters were labeled using different colors. We found that journals focusing on the same research field tend to aggregate in the same cluster; these research fields include

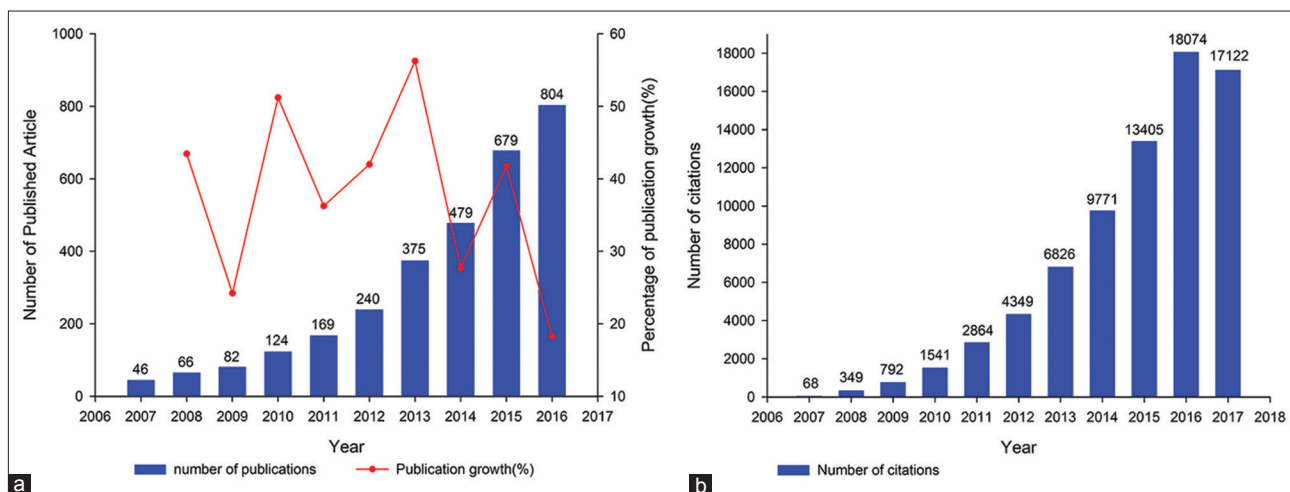


Figure 1: Publication outputs and citation number of articles related to macrophage polarization from 2007 to 2016. (a) Annual publication number and publication growth rate; (b) annual citation number.

Table 1: Top 21 journals in the field of macrophage polarization ranked by publication number

Ranking	Journal title	Impact factor in 2016	Country	Records	Total citations	Average citation per paper
1	<i>PLOS ONE</i>	2.806	USA	197	4277	21.71
2	<i>J IMMUNOL</i>	4.856	USA	141	5107	36.22
3	<i>SCI REP-UK</i>	4.259	England	83	532	6.41
4	<i>J BIOL CHEM</i>	4.125	USA	65	2046	31.48
5	<i>ONCOTARGET</i>	5.168	USA	53	401	7.57
6	<i>J LEUKOCYTE BIOL</i>	4.018	USA	45	1024	22.76
7	<i>BIOMATERIALS</i>	8.402	The Netherlands	43	1986	46.19
8	<i>P NATL ACAD SCI USA</i>	9.661	USA	41	2395	58.41
9	<i>EUR J IMMUNOL</i>	4.227	USA	39	1190	30.51
10	<i>DIABETES</i>	8.684	USA	38	2093	55.08
11	<i>ARTERIOSCL THROM VAS</i>	6.607	USA	35	1319	37.69
12	<i>INT IMMUNOPHARMACOL</i>	2.956	The Netherlands	28	236	8.43
13	<i>INFECT IMMUN</i>	3.593	USA	25	466	18.64
14	<i>BLOOD</i>	13.164	USA	25	1304	52.16
15	<i>IMMUNOBIOLOGY</i>	2.720	Germany	24	412	17.17
16	<i>MEDIAT INFLAMM</i>	3.232	England	23	96	4.17
17	<i>J NEUROINFLAMM</i>	5.102	England	23	351	15.26
18	<i>ACTA BIOMATER</i>	6.319	England	23	533	23.17
19	<i>J CLIN INVEST</i>	12.784	USA	22	4535	206.14
20	<i>FASEB J</i>	5.498	USA	22	466	21.18
21	<i>ONCOIMMUNOLOGY</i>	7.719	USA	21	151	7.19

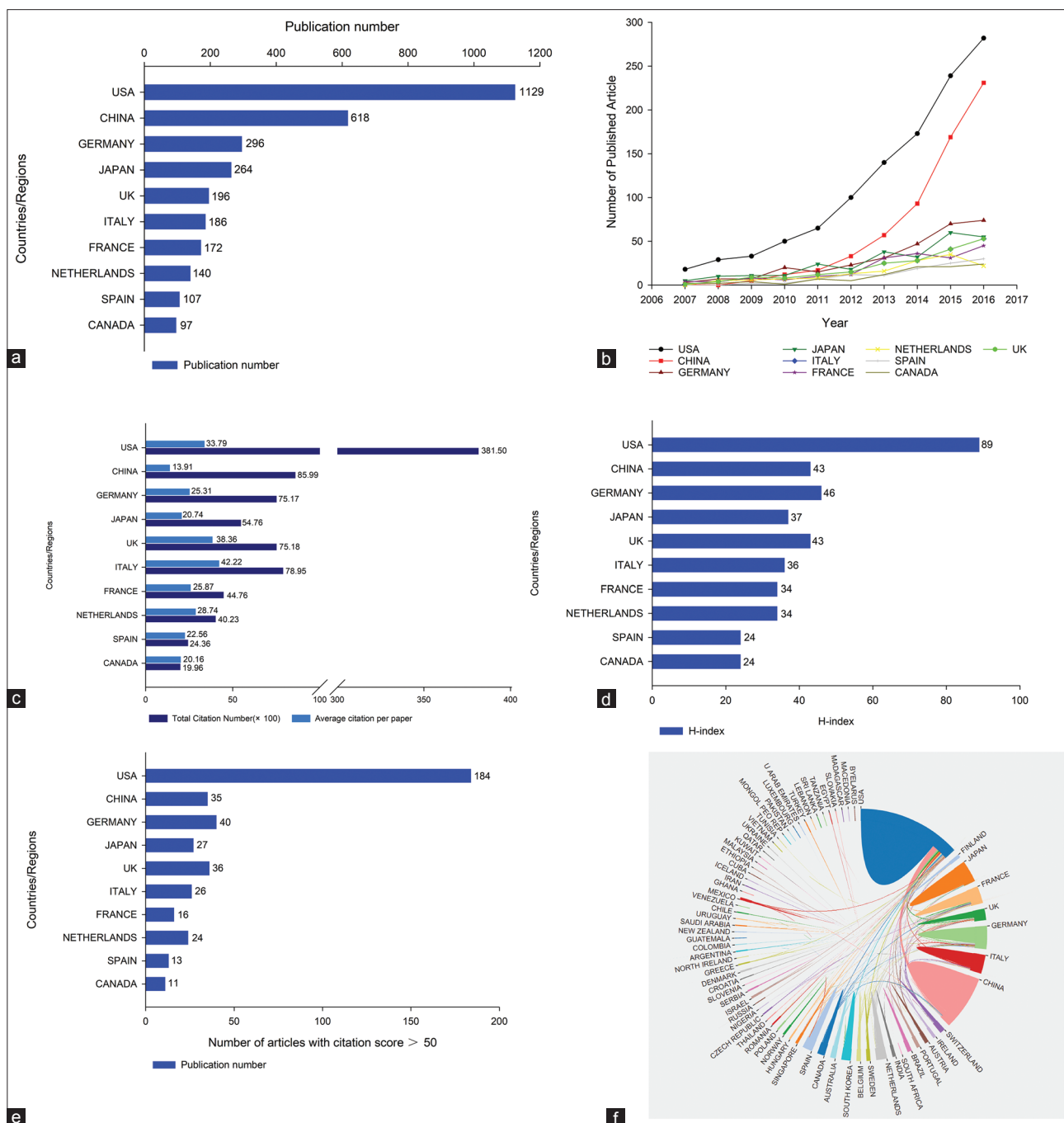


Figure 2: Contributions of the top 10 most productive countries/regions to macrophage polarization research. (a) Publication number; (b) annual publication number growth; (c) total citation number and average citations per paper; (d) H-index; (e) number of articles with a citation score > 50; (f) international collaboration.

biomaterials, neuroscience, tumor biology, and diabetes. We therefore postulate that macrophage polarization might be involved in either physiological or pathological process in these fields.

Research subject categories

The subject categories of these articles were also reviewed. The most common was “immunology,” followed by “science technology other topics,” “biochemistry molecular biology,” and “oncology” [Figure 3c]. All the subject categories were defined on the basis of their description on Web of Science.

Citation network among core authors and institutional productivity

The most highly cited researchers and the productive institutions were revealed in our study. There were a total of 17,615 authors on the 3064 articles, and the average number of authors per paper was 5.75. The local citation and global citation scores of these authors were analyzed with HistCite software. The local citation score represents how many times the author’s relevant papers have been cited by other papers also in the collection, whereas the global citation score represents how many times the

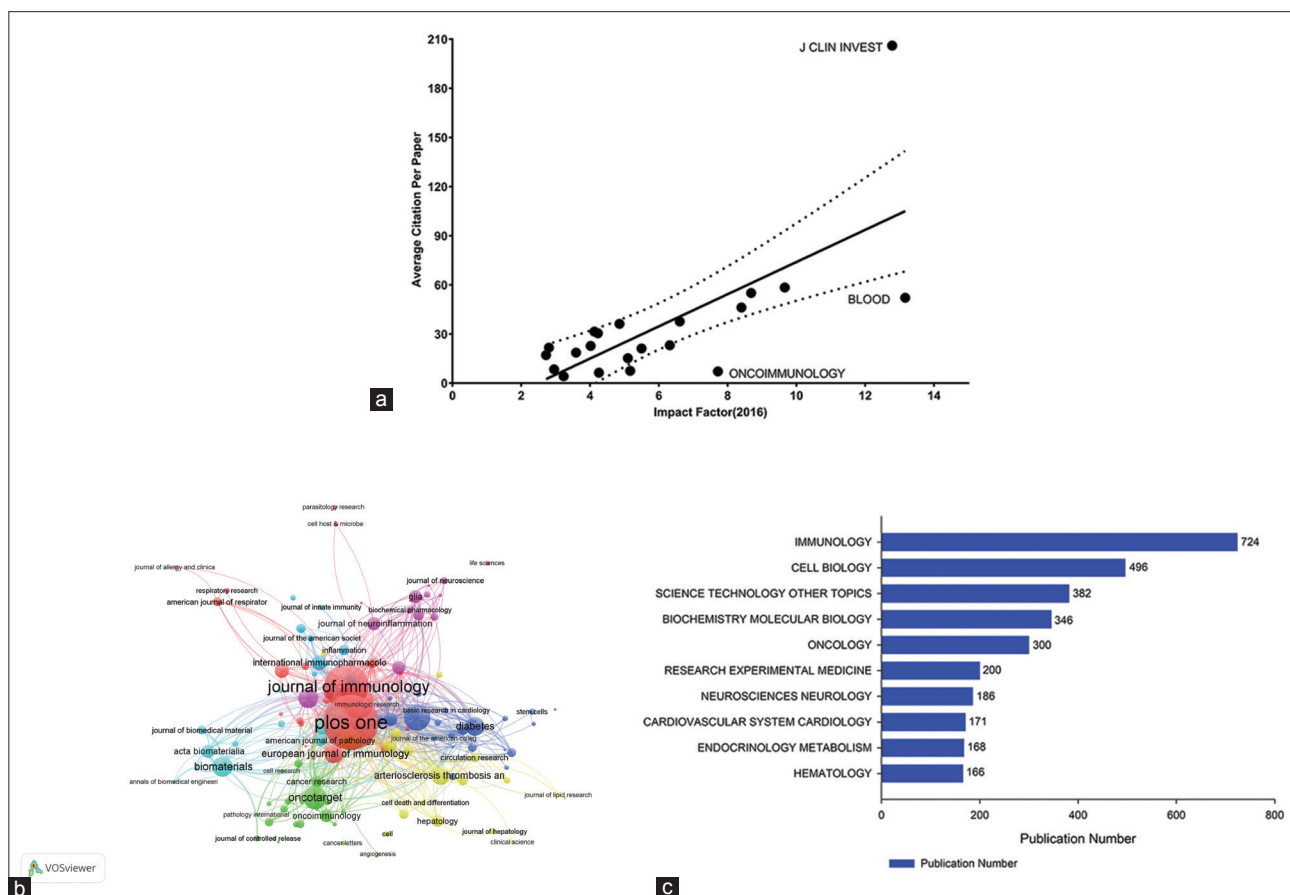


Figure 3: Distributions of articles between journals and subject categories. (a) Regression analysis between the impact factor and average citations per paper among the top 21 journals; (b) citation network and clusters of the top 122 highly cited journals; (c) publication number of the top 10 most frequently appearing subject categories.

author’s relevant papers have been cited by all the papers in the database.

In this study, we defined a “core researcher” as one whose papers have received over 400 citations (global citation score >400). The co-authorship and citation network among core authors was also analyzed [Figure 4a and 4b]. In this figure, authors were represented by dots, and larger dots indicate higher author global citation scores. Some important research teams were clearly revealed. Mantovani, Sica, Lumeng, and Locati have made many contributions to this field, because their papers were frequently cited by other core researchers. Mantovani, Sica, and Locati worked together on many papers, whereas their collaborations with Lumeng were not as frequent.

Among the top 20 most productive institutions, 9 are located in the USA, 4 in China, and 3 in France. Harvard University published 70 articles in this field, followed by the University of Michigan, Fudan University, the University of Pittsburgh, and Shanghai Jiao Tong University. Articles from the University of Milan were cited 135.43 times on average, which was much higher than others [Figure 4c]. This was partly due to three highly cited authors, Mantovani, Sica, and Locati, who all listed the University of Milan as their affiliation in many articles.

Forty out of 2779 institutions had published over 20 articles each relating to macrophage polarization, so collaboration between them was analyzed. Institutions in the USA frequently worked internationally. There was close collaboration between the University of Pittsburgh and Fudan University in China, as well as between the University of Pennsylvania and Milan University in Italy. Cross-institutional collaboration in other countries was mainly intranational. For example, in China, Huazhong University of Science and Technology, Wuhan University, Sun Yat-sen University, and Nanjing University worked in close collaboration [Figure 4d].

Keywords and MeSH terms

The development of keywords over time was analyzed to obtain a full picture of the frontiers and hotspots in macrophage polarization research. A cluster visualization of MeSH terms was performed with VOSviewer. Four keywords in our study were excluded to get a better view; these were “macrophage,” “macrophage polarization,” “polarization,” and “macrophage polarization.” Schematically, each keyword was represented by a circle that was partitioned into rings of different colors, with each ring representing a different time slice of 1-year and the sizes of the circles and rings being proportional to how many times the keyword had shown up.

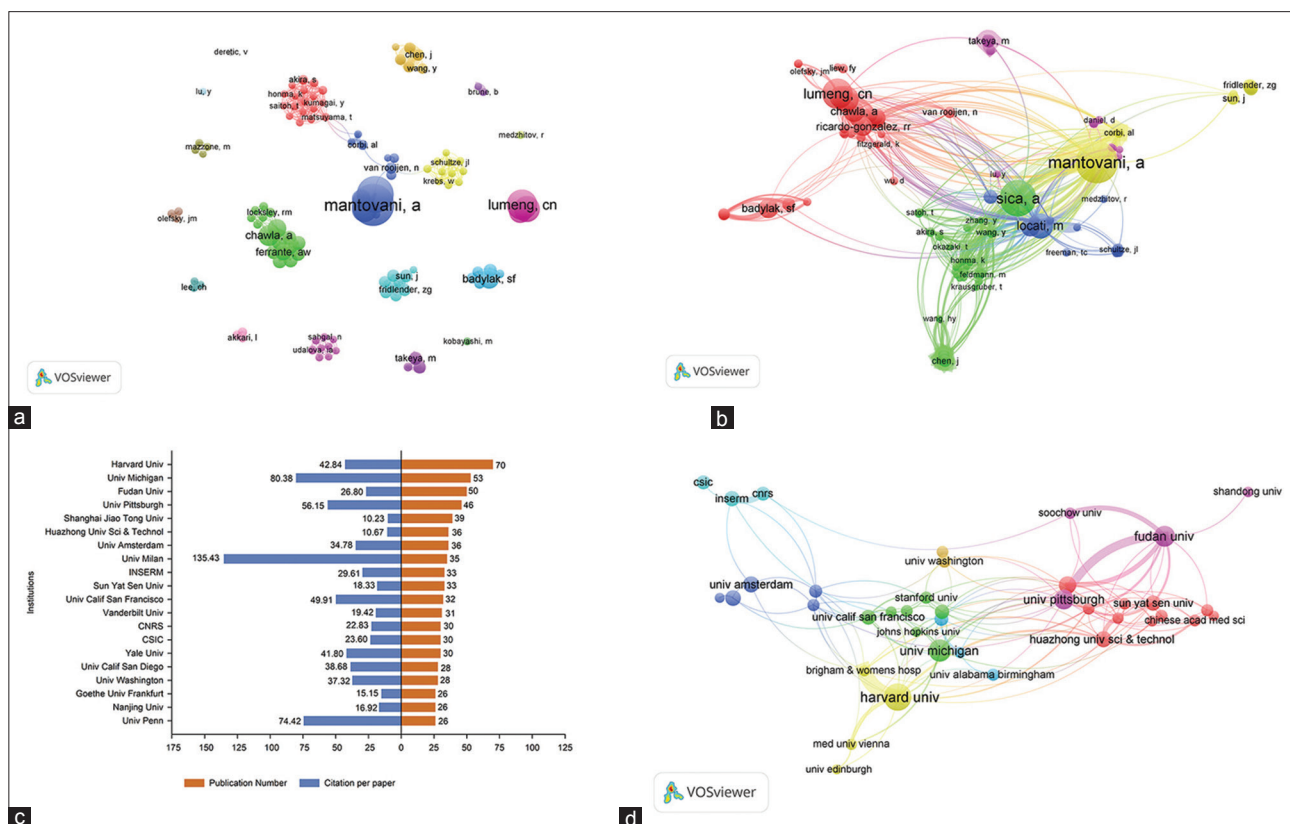


Figure 4: Collaboration and citation networks among core authors and institutions. (a) Co-authorship among core authors; (b) citation network among core authors; (c) top 20 institutions that produced the largest number of articles; (d) collaboration between institutions.

Most keywords in this research field were first used in the years 2007 and 2008. However, some appeared much later, such as “injury” and “metastasis” in 2011, “microglia” in 2013, and “fibrosis” in 2014 [Figure 5a]. These keywords are indicative of the frontiers of macrophage polarization research.

All MeSH terms were divided into five clusters [Figure 5b], and “tumor,” “infection,” and “obesity” were the most prominent. They were also promising hotspots of macrophage polarization research related to “dendritic cell,” “injury,” “CD163,” “CD68,” “deficiency,” “mice,” and “macrophage infiltration” [Figure 5c]. This information may be useful to researchers entering this field.

DISCUSSION

In this study, 3064 publications on macrophage polarization research were retrieved using the online database Web of Science. Only 46 articles were published in the year 2007, and a large increase in annual output was seen thereafter, indicating that macrophage polarization research is attracting interest and therefore growing rapidly. Macrophage polarization may remain a research hotspot for the next few years.

Studies conducted in the USA and China accounted for 57.0% (1747) of the publications, making these nations the main force pushing this research forward. The USA and

China are the only two countries that have demonstrated accelerating publication growth in the past 10 years, whereas the growth rate of other productive countries remains slow. The rise in the output of these two countries can be attributed to the allocation of greater funds to this area and consequently the interest of more scientists.

The H-index and highly cited article number of the USA were far beyond those of the other countries, indicating that many exciting and important contributions were made in the USA. The total citation number of the USA also ranked first as a result of its leadership in both publication number and impact.

Studies conducted in China were cited for 13.91 times on average, ranking last among the 10 most productive countries. However, the H-index and highly cited article number for China were 43 and 35, respectively, which were lower than the USA and Germany.

The journal distribution of the articles was highly centralized since one-third was published in just 21 journals. All these journals are published in developed countries. Two-thirds (14 out of 21) of these, including three high-impact journals (IF >10), are based in the USA, emphasizing the irreplaceable role the USA plays in academic publication in this field. For most of the 21 journals, the average citation of macrophage polarization papers was much higher than the IF of the journal. This supports our contention that macrophage polarization is a

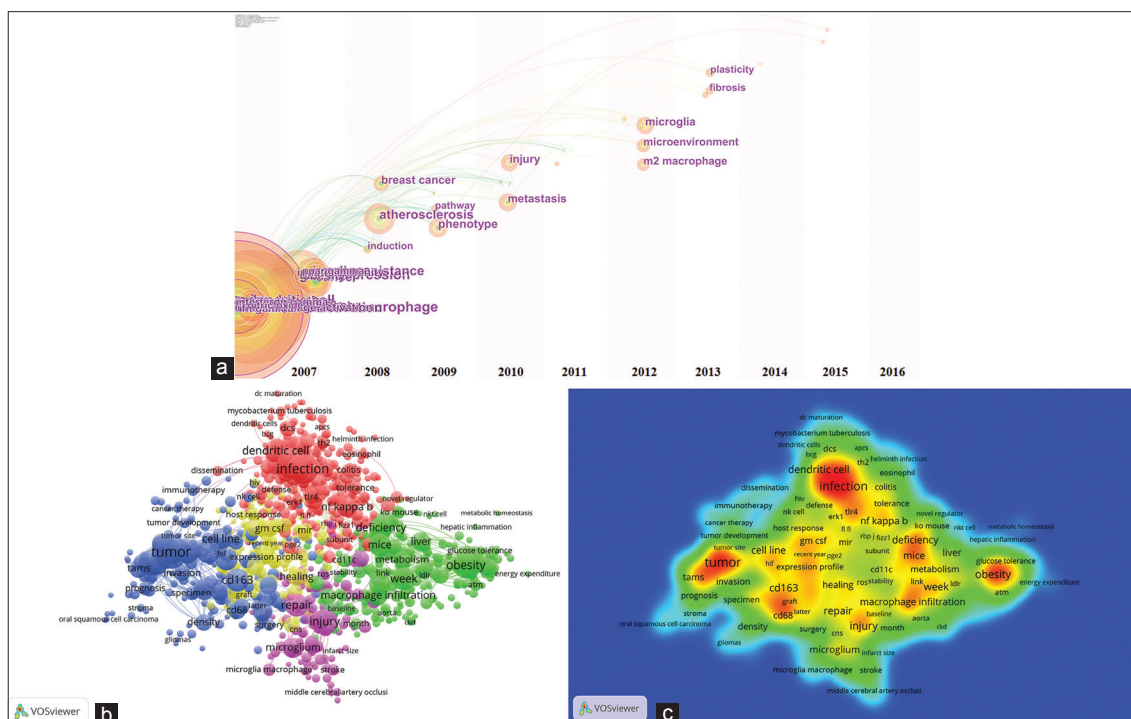


Figure 5: Keywords and MeSH terms linked to macrophage polarization research. (a) Time-zone view of keywords; (b) network visualization of MeSH terms; (c) heat map of MeSH terms.

focused area of research, since papers in this field are either cited frequently or attracted citations for several years after publication.

In a citation network, journals in different clusters tend to focus on different subjects. For example, *Biomaterials* and *Acta Biomaterialia* focus on biomaterials; *Oncotarget* and *Cancer Research* prefer to publish research on tumors; and *Arteriosclerosis, Thrombosis, and Vascular Biology* and *Cardiovascular Research* prefer cardiology-related articles. These subjects all have close associations with macrophage polarization.

As time has passed, some new frontiers attracted attention. They are “microglia,” “fibrosis,” “metastasis,” “injury,” and others. Researches on the relationship between macrophage polarization and tumor, infection, and obesity are promising areas.

In conclusion, research on macrophage polarization has grown rapidly in the last 10 years and will hopefully remain a hot topic for a few years to come. The USA has taken the lead in this field from 2007 to 2016 by publishing one-third of the total and most of the highly cited articles. *PLOS One*, *Journal of Immunology*, and *Scientific Reports* were the top three journals with the highest publishing number. Immunology accounted for the largest number of publications with respect to subject categories. Mantovani, Sica, Lumeng, and Locati were the most highly cited authors and have produced some fundamental papers in this field. Harvard University published most articles, followed by the University of Michigan, Fudan University, the University of Pittsburgh,

Shanghai Jiao Tong University, and others. Insulin resistance, atherosclerosis, obesity, and metastasis were found to be frontiers in macrophage polarization research, and tumors, infection, and obesity are the most promising hotspots.

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Conflicts of interest

There are no conflicts of interest.

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巨噬细胞极化研究趋势的文献计量学分析

摘要

背景: 巨噬细胞极化参与许多疾病的发生发展过程, 例如肥胖、糖尿病和癌症。本研究旨在理解巨噬细胞极化的研究趋势和研究热点。

方法: 我们检索了科学网核心合集 (WoSCC) 数据库以获得本研究领域的原创性文献, 使用软件Citespace, Histcite和VOSviewer对该领域的科学产出及研究趋势进行分析, 并将其可视化。

结果: 本研究共纳入3064篇文献, 年文献发表量呈指数增长趋势。这些文献共被引用74801次, 在最近10年内, 年度被引次数从68次增长至18074次。共有76个国家参与了巨噬细胞极化的相关研究, 美国以1129篇文献 (占总数的36.8%) 占据了国家科研产出榜的首位。美国发表的文献也拥有最高的H指数, 总被引次数和高被引文献数。*PLOS One*, *Journal of Immunology* 和 *Scientific Reports* 是该领域内发表文献数量最多的三份杂志。通过对杂志间相互引用状况进行分析, 我们发现了与巨噬细胞极化相关的多个跨学科研究领域, 例如生物材料、肿瘤和糖尿病。发文量最多的20家科研机构主要位于美国、法国和中国, 被引次数最多的作者主要来自美国和意大利。肿瘤、肥胖和感染是巨噬细胞极化相关的研究热点, 在未来数年中可能值得关注。

结论: 本研究提供了一份综合性分析, 以描述巨噬细胞极化研究的科学产出, 研究合作和研究热点。