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ORIGINAL RESEARCH

Global Trends and Hotspots of Transient Receptor Potential Melastatin 8 Research from 2002 to 2021: A Bibliometric Analysis

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Background: Transient receptor potential channels are the major temperature and nociceptive receptors in the human body and transient receptor potential melastatin 8 (TRPM8) is the cold-sensitive and non-selective cation channel. In our study, we performed a bibliometric analysis of TRPM8 from 2002 to 2021 to summarize the current research status and potential research direction in the future.

Methods: The TRPM8-related publications were selected from the Web of Science Core Collection SCI-EXPANDED database from 2002 to 2021. The publication details, such as authors, titles, and author keywords, were used for bibliometric analysis and network visualization to present the current state of TRPM8 research.

Results: A total of 1035 articles met the inclusion criteria. The number of TRPM8-related articles has grown rapidly over the past two decades. The USA has the largest number of publications, citations, and international collaborations. The TRPM8-related articles are mainly published and cited in neurological journals, such as the Journal of Neuroscience (41 publications and 2171 local citations). Prevarskaya N. has the most publications (26), and Patapoutian A. has been cited the most (1414 local citations). The popular disciplines in TRPM8 research include Neurosciences and Neurology, Pharmacology and Pharmacy, Biochemistry, and Molecular Biology. Research hotspots are mainly TRP channel, calcium, prostate cancer, proliferation, pain, cold, nociception, and inflammation.

Conclusion: Our bibliometric analysis demonstrates that the number of TRPM8 studies has increased from 2002 to 2021. The global research trends and hotspots include the activation mechanism of TRPM8 in neurons, the role of TRPM8 in neuronal and non-neuronal diseases, and therapeutic target research.

Keywords: TRPM8, TRP channel, calcium influx, cold-sensitive receptor, nociceptive receptor, therapeutic target

Introduction

Transient receptor potential (TRP) channels are the body's main temperature and nociceptive receptors. Their discoverers, David Julius and Ardem Patapoutian have been awarded the 2021 Nobel Prize in Physiology or Medicine.[1] TRP melastatin 8 (TRPM8) is a cold-sensitive and non-selective cation channel that mainly induces extracellular calcium influx.[2] It can be activated by cold temperature, membrane depolarization, and different chemical materials such as menthol and icilin.[2,3] TRPM8 is highly expressed on various neurons and non-excitable cells, such as peripheral sensory neurons, kidney cells,[4] human lung epithelial cells,[5] bladder,[6] non-neuronal part of the cornea,[7,8] and macrophages.[9,10] In addition, several studies have demonstrated that TRPM8 is optimally expressed in luminal cells of prostatic epithelium (normal tissue),[11,12] and further increased in primary prostate cancers.[12,13] TRPM8 is currently an emerging direction of neurosciences, cancer research, and (other) non-neurological diseases (such as kidney-, lung-, ocular, or pancreatic diseases).[1,4–8]

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Bibliometric analysis is an effective method for quantitative analysis of scientific research at global, national, institutional, and individual levels.[14,15] In recent years, it has been used in different disciplines to analyze the progress, trends, and hotspots in specific research fields.[16] Playing a vital role in the development of the discipline, bibliometric analysis helps to deepen the understanding of knowledge and fill the gap in this field.[17] It can also foster academic collaboration among scholars with similar interests in a particular field of study.[18] As one of the major databases used to retrieve publications in bibliometric analysis, the Web of Science Database covers a wide range of high-quality literature and provides comprehensive data for the analysis.[19] BiblioShiny (Bibliometrix) and VOSviewer are always used for networking, graphing, and visualization of bibliometric analysis to identify the most influential countries, institutions, scholars, journals, and articles.[20] The results not only show the global trends and hotspots in specific research fields, sort out the research direction for scholars, but also display the most recognized authors and articles in this field, thus helping young researchers quickly become familiar with the basic knowledge of this field.

TRPM8 exists in various cell types and is regarded as the potential therapeutic target for some diseases, such as migraine, cancer, and colitis.[9,21,22] In our study, a bibliometric analysis was performed to outline the current status of relevant publications and assess the countries, institutions, authors' connections, and research trends in this research area. Our findings will point out the TRPM8 research directions for future work.

Materials and Methods

Literature Collection Strategy

This is a retrospective study that evaluates data published online and in libraries and therefore does not require the approval of the institutional review committee. We used the Web of Science (WoS) Core Collection Science Citation Index Expanded (SCI-EXPANDED) database (Clarivate, London, England) to conduct a comprehensive search from 2002 to 2021. "TRPM8" or "TRPM 8" or "Transient receptor potential melastatin 8" was searched in Title or Abstract or Author Keywords (available publications=1460). The language was restricted to English (available publications=1456) and the document type was restricted to the original article (available publications=1041).[23]

All basic information of the included articles, including title, abstract, author, author keywords, source, language, and citation, were downloaded from the WoS Core Collection SCI-EXPANDED database in text format.[24,25] Two authors independently screened the retrieved articles and determined their availability. 6 articles that were published in 2022 have been removed (available articles=1035).

Bibliometric Analysis

The qualified information of retrieved publications was imported to BiblioShiny software (the bibliometrix package in R 4.2.0)[24,26] to automatically convert and analyze bibliographic data, including global trends, national/ institutional/ sources distribution, historical direct citation network, top 20 of international collaborations, most cited countries, most relevant countries/ affiliations/ sources/ authors, most local cited sources/ authors/ documents/ references, thematic map of author keywords clusters, and most global cited documents. All results were exported directly from BiblioShiny, and all tables were exported from BiblioShiny in Microsoft Excel (Version 2204) for further editions. We employed VOSviewer (Version 1.6.16, Leiden, the Netherlands) to analyze the data and construct the network of co-authorship and co-occurrence of author keywords.[20,24,27] Each author had more than or equal to 5 articles (149 authors in total and 124 authors had links), and each author keyword occurred more than or equal to 5 times (132 keywords in total). The data was displayed in three forms: network, overlay, and density visualization. In the network map, colors indicated clusters, and lines indicated cooperation or co-occurrence. The occurrence number of the author or author keyword was represented by the circle size, and the strength of the link was represented by the line thickness. In the overlay map, colors indicated the average published year which is displayed in time scale. In the density map, the yellow color indicated the most frequently occurring author keyword in the TRPM8 research field.

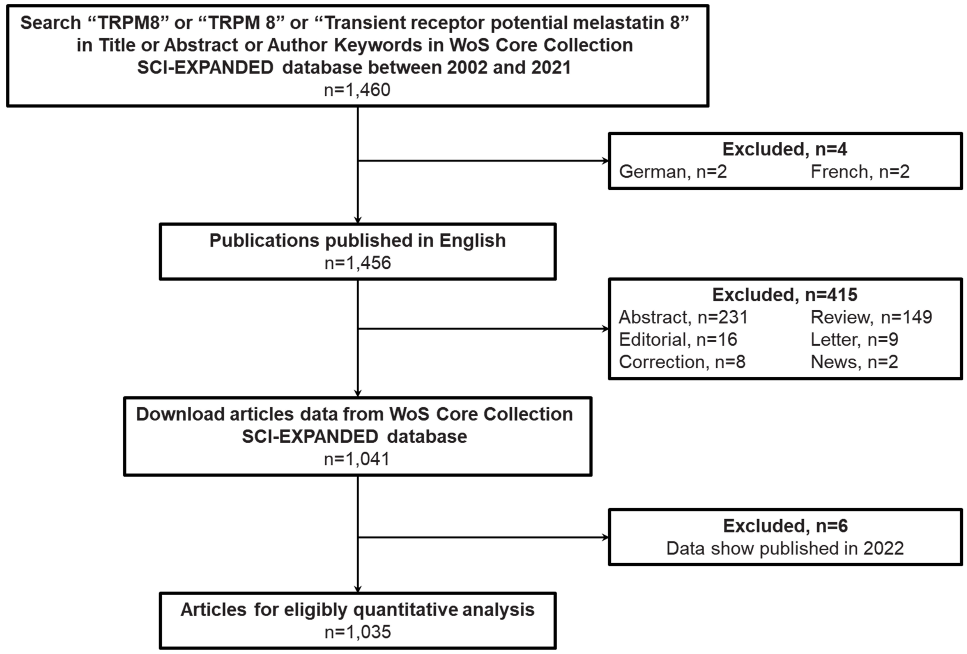

Figure 1 Flowchart for screening publications.
Abbreviations: WoS, Web of Science; SCI-EXPANDED, Science Citation Index Expanded.

Results

The Global Trend of TRPM8 Research

Between 2002 and 2021, we identified a total number of 1460 publications related to TRPM8, of which 4 non-English publications were excluded (Figure 1). Additional 415 publications were removed because of non-target article types, including 231 meeting abstracts, 149 review articles, 16 editorial materials, 9 letters, and 10 other types. 6 articles were excluded due to the data showing published in 2022 (Figure 1). Finally, 1035 articles were used for eligible bibliometric analysis.

We used BiblioShiny to analyze the 1035 finely screened articles on TRPM8 over the past two decades. Results show that the TRPM8-related articles increased from 3 in 2002 to 79 in 2021, and the annual growth rate reached 18.79% (Figure 2A). The results illustrated a strong growth trend of global publications in the TRPM8 research area. Furthermore, the citations of publications in 2002 decreased from a total of 2803 (an average of 46.7 citations per article per year) to a total of 213 citations in 2021 (an average of 2.7 citations per article per year) (Figure 2B). Considering the citations were affected by the publishing year, it was normal for citations to decrease as the year increased.

Distribution of Countries and Institutions

Global contributions to TRPM8 research were represented in a map with global collaboration lines (Figure 3A). A total of 52 countries have contributed to this field. With the corresponding author's country, the USA had the largest number of articles (267), followed by Japan (132), China (124), Germany (81), and England (61) (Figure 3B, Table S1). Furthermore, the USA also had the most citations (21,646), followed by Japan (4783), England (3245), Germany (2739), Belgium (2255), and China (2035) (Figure 4A). Regarding international collaboration, scholars from the USA and China have the most international collaborations (31), followed by the USA and Germany (19 times), the USA and England (16 times), the USA and Japan (14 times), and the USA and Canada (12) (Figure 3A–C, Table S2). Our results showed that scholars in the USA played a leading role in the TRPM8 research area, and have the most frequent collaboration with scholars from other countries.

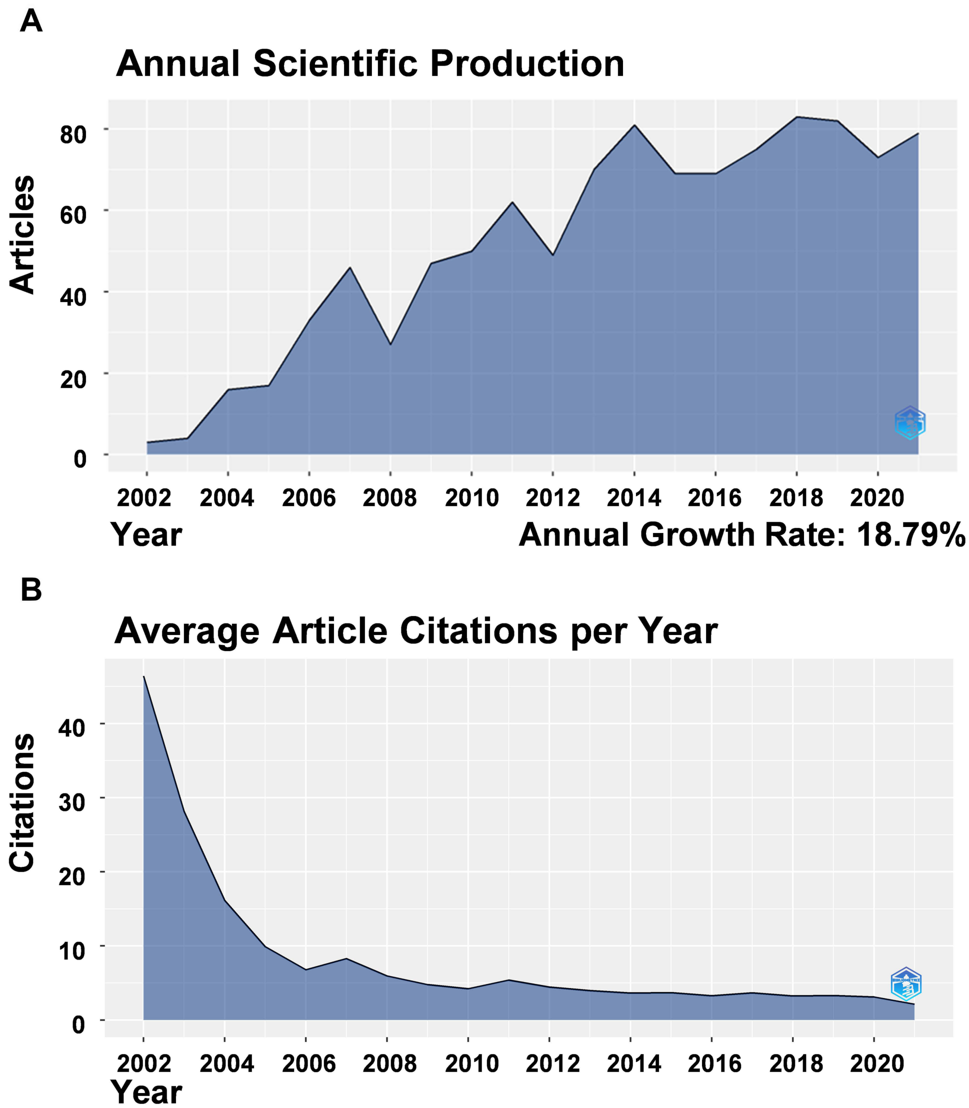

Figure 2 Global trend in TRPM8 research over the past two decades. (**A**) Annual scientific production from 2002 to 2021. (**B**) Average article citations per year from 2002 to 2021.

A total of 1163 institutions were involved in the publications on TRPM8. The University of Washington and Katholieke Universiteit Leuven contributed the largest number of articles (37 and 33 per institution), followed by Universidad Miguel Hernández (31), University of Southern California (31), University of Florida (29), and Zhejiang University (24) (Figure 4B). Most of the institutions are located in the USA, followed by Japan and China (Figure 4C). Universidad Miguel Hernández had the most institutional collaborations (Figure 4D). The global trends of TRPM8-related institutional collaborations were characterized by decentralized cooperation (Figure 4D).

Distribution of Sources and Authors

All 1035 articles about TRPM8 were published in a total of 388 sources. Journal of Neuroscience published the largest number of articles (41), followed by PLOS ONE (38), Journal of Biological Chemistry (32), Molecular Pain (25), and Scientific Reports (23) (Figure 5A). A total of 25,317 references (4052 journals) were cited in the 1035 articles. Nature has been locally cited the most (2564 times), followed by the Journal of Neuroscience (2171 times), Journal of Biological Chemistry (1679 times), Neuron (1402 times), and Cell (1311 times) (Figure 5B). In addition, we analyzed the most co-cited 50 journals and displayed them as a network (Figure 5C). Three obvious clusters were presented: the first was

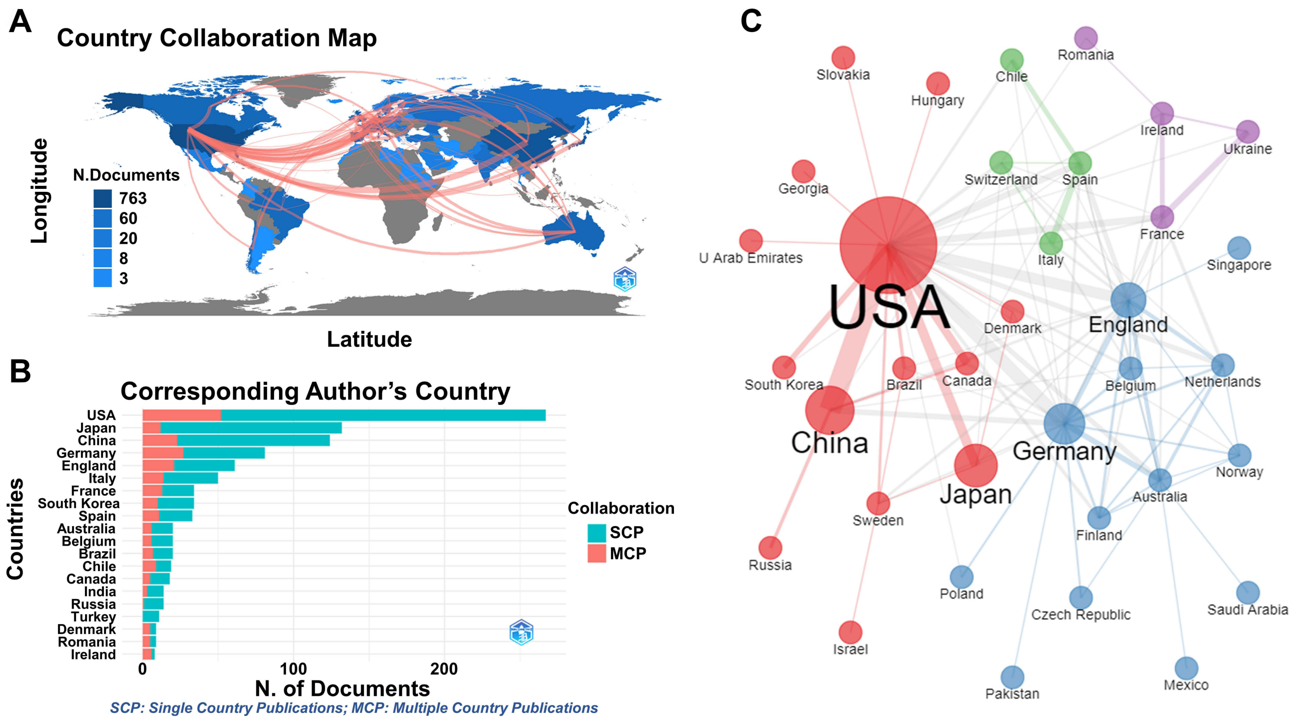

Figure 3 Distributions of countries. (**A**) World map showing collaboration and the volume of publications by country. (**B**) Top 20 corresponding author's countries with the most publications. (**C**) Network of country collaborations (different colors indicated clusters, circle size indicated volume of publications, the thickness of lines indicated total collaboration strength).

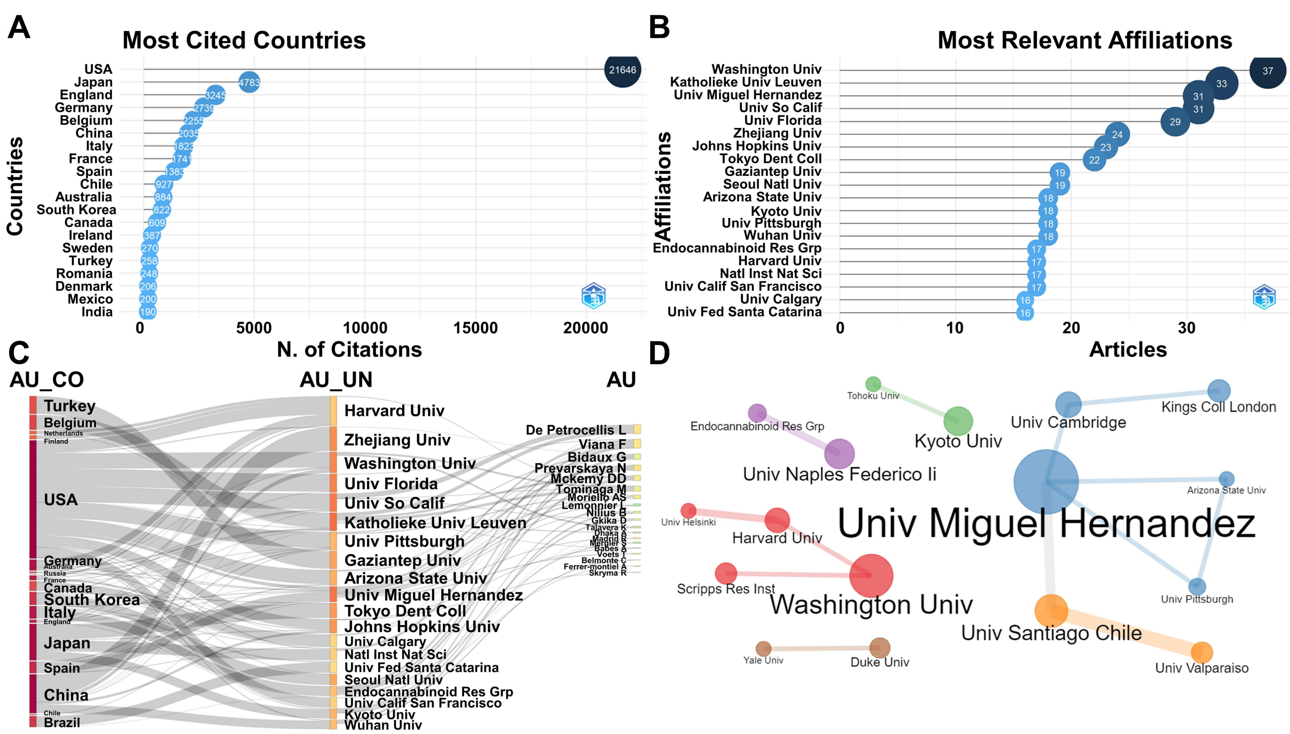

Figure 4 Distributions of countries and institutions. (**A**) Top 20 countries with the most article citations. (**B**) Top 20 institutions with the most publications. (**C**) Three-fields plot among countries (AU_CO), institutions (AU_UN), and authors (AU). (**D**) Network of institutional collaborations.

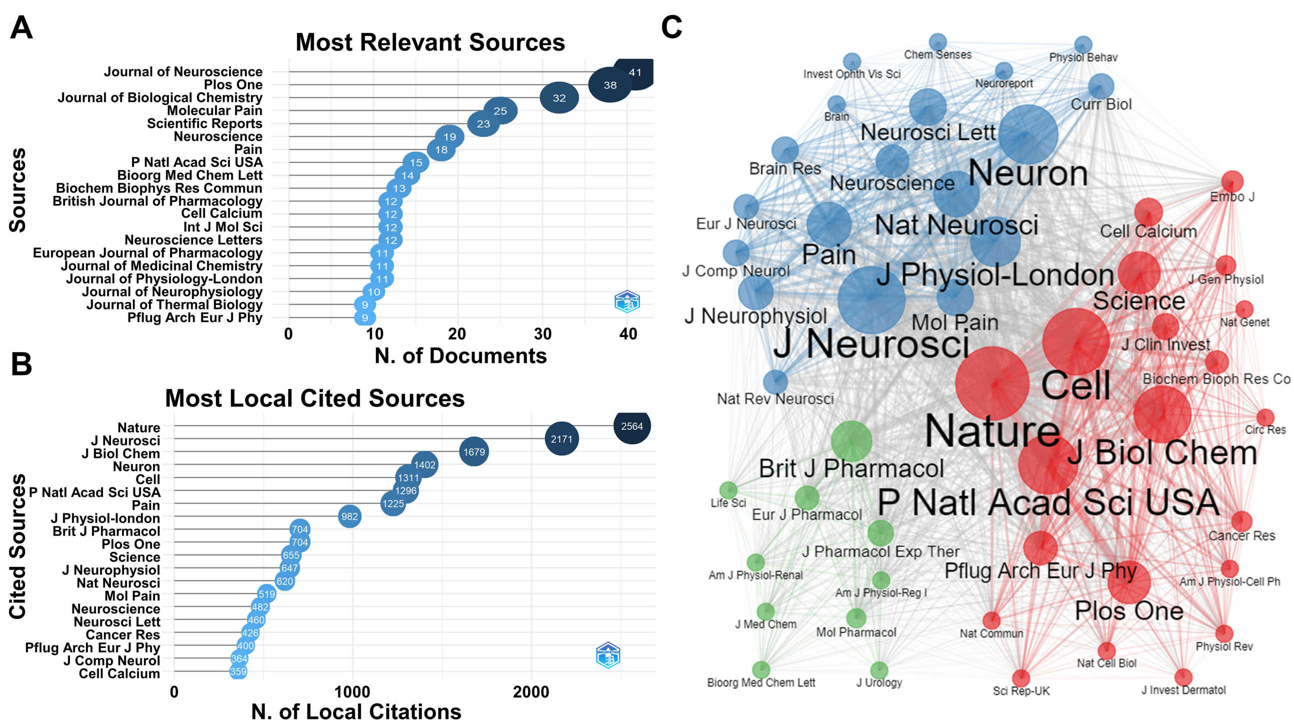

Figure 5 Distributions of journals. (**A**) Top 20 journals with the most publications. (**B**) Top 20 journals local cited by related articles (from reference lists). (**C**) Network of the top 50 co-citation journals cited by related articles.

dominated by Nature, Cell, Journal of Biological Chemistry, Proceedings of the National Academy of Sciences of The United States of America; the second was dominated by Journal of Neuroscience, Neuron, Pain, Nature Neuroscience, Journal of Physiology-London; the third was dominated by British Journal of Pharmacology, European Journal of Pharmacology, and Journal of Pharmacology and Experimental Therapeutics (Figure 5C).

A total of 4799 authors published articles in the TRPM8 research field. Prevarskaya N. was the most productive author (26), followed by Viana F. (21), De Petrocellis L. (21), Voets T. (18), Mckemy D. D. (17), Moriello A. S. (17), and Tominaga M. (17) (Figure 6A). We analyzed the total local citations of these 4799 authors. Results showed that Patapoutian A., the Nobel laureate, was most cited locally (1414 times), followed by Earley T. J. (1212 times), Story G. M. (992 times), Bevan S. (938 times), and Andersson D. A. (938 times) (Figure 6B). Furthermore, we analyzed the co-authorship between authors with five publications or more (149 authors) and removed the unconnected 25 authors. 124 authors were included in the networks with clusters or average publication years (Figure 6C and D). The six authors with the most co-authorships were Prevarskaya N. (total link strength, 140), Bidaux G. (99), Skryma R. (90), Lemonier L. (70), Shuba Y. and Gkika D. (68). Ferrer-Montiel A. and the authors around him published articles after 2016, in green or yellow colors (Figure 6D).

Distribution of Articles and Author Keywords

All 1035 finely screened articles have been globally cited 47,732 times and locally cited 10,038 times. The most globally cited article was a research about the discovery of transient receptor potential ankyrin 1 (TRPA1), another cold-sensitive TRP channel, and the authors compared the sensitive temperature between TRPA1 and TRPM8 (1759 citations in total),[28] published in Cell 2003 by Gina M. Story and correspondence to Ardem Patapoutian, the Nobel laureate (Figure 7A). The most locally cited article was a research about the discovery of TRPM8 (521 citations in total),[29] which was published in Cell 2002 by Andrea M. Peier and also correspondence to Ardem Patapoutian (Figure 7B). The most globally or locally cited 20 articles were shown in Table S3 and S4. A total of 25,317 references were cited in these 1035 articles, the most locally cited reference was another research about the discovery of TRPM8 (548 citations in total),[30] which was published in Nature 2002 by David D. McKemy and correspondence to David Julius, another Nobel laureate (Figure 7C). The historical direct citations of the most 20 locally cited articles from 2002 to 2021 were presented as a network with time annotations (Figure 7D).

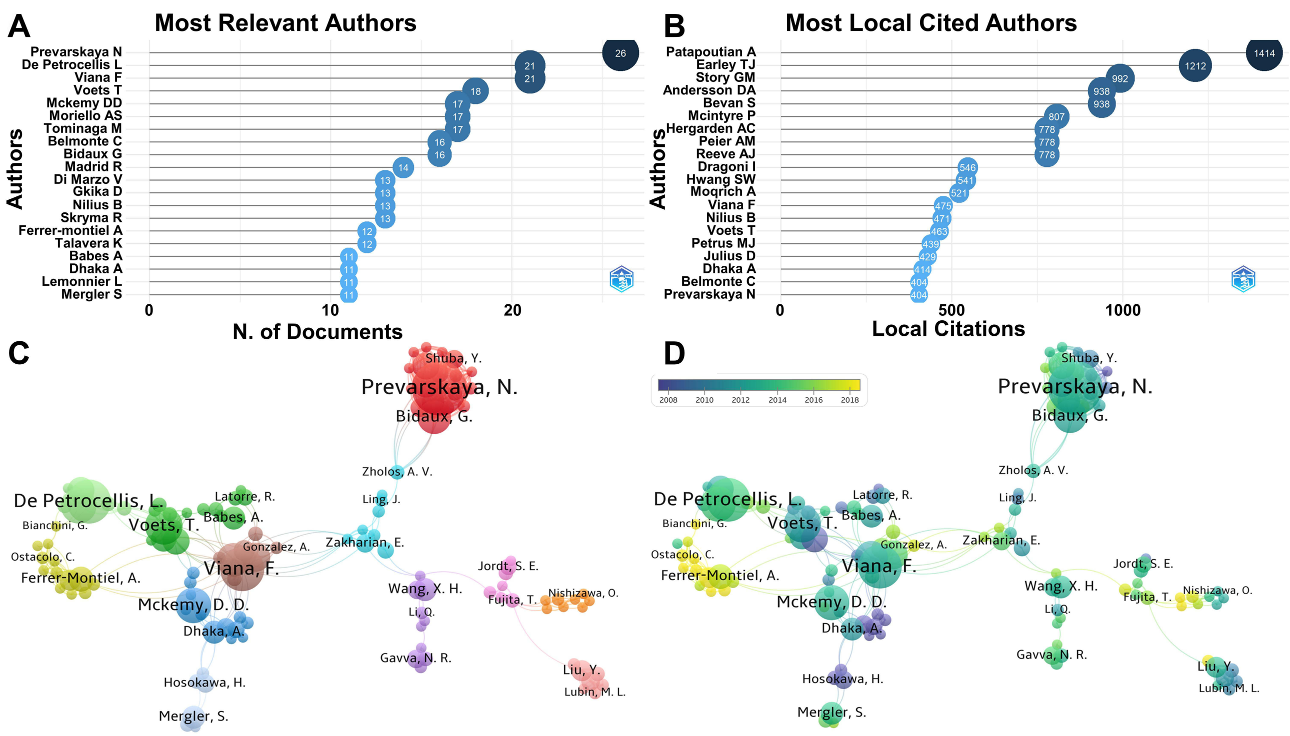

Figure 6 Contributions of authors. (**A**) Top 20 authors with the most publications. (**B**) Top 20 authors with the most local citations. (**C**) Network of co-authorship. (**D**) Network of co-authorship from 2002 to 2021 with average publication year.

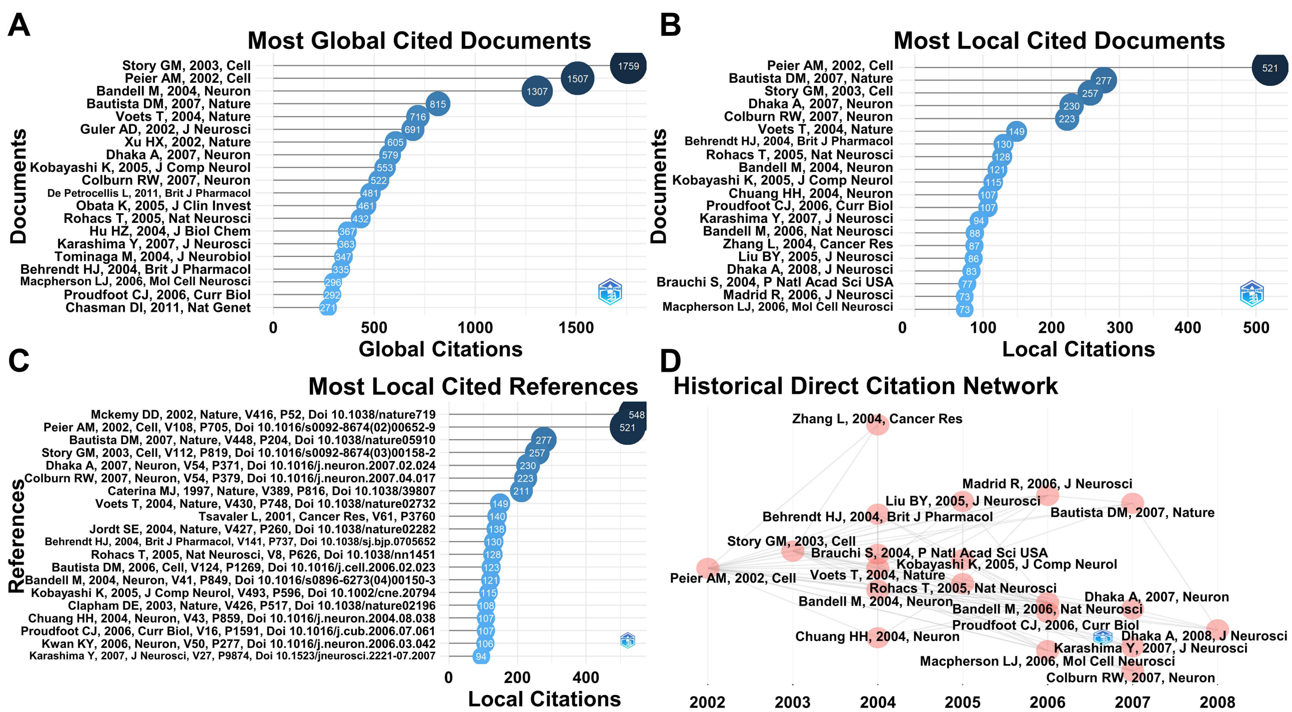

Figure 7 Distributions of articles. (**A**) Top 20 articles with the most global citations. (**B**) Top 20 articles with the most local citations. (**C**) Top 20 references with the most local citations. (**D**) Network of historical direct citation with the top 20 most local cited articles from 2002 to 2021.

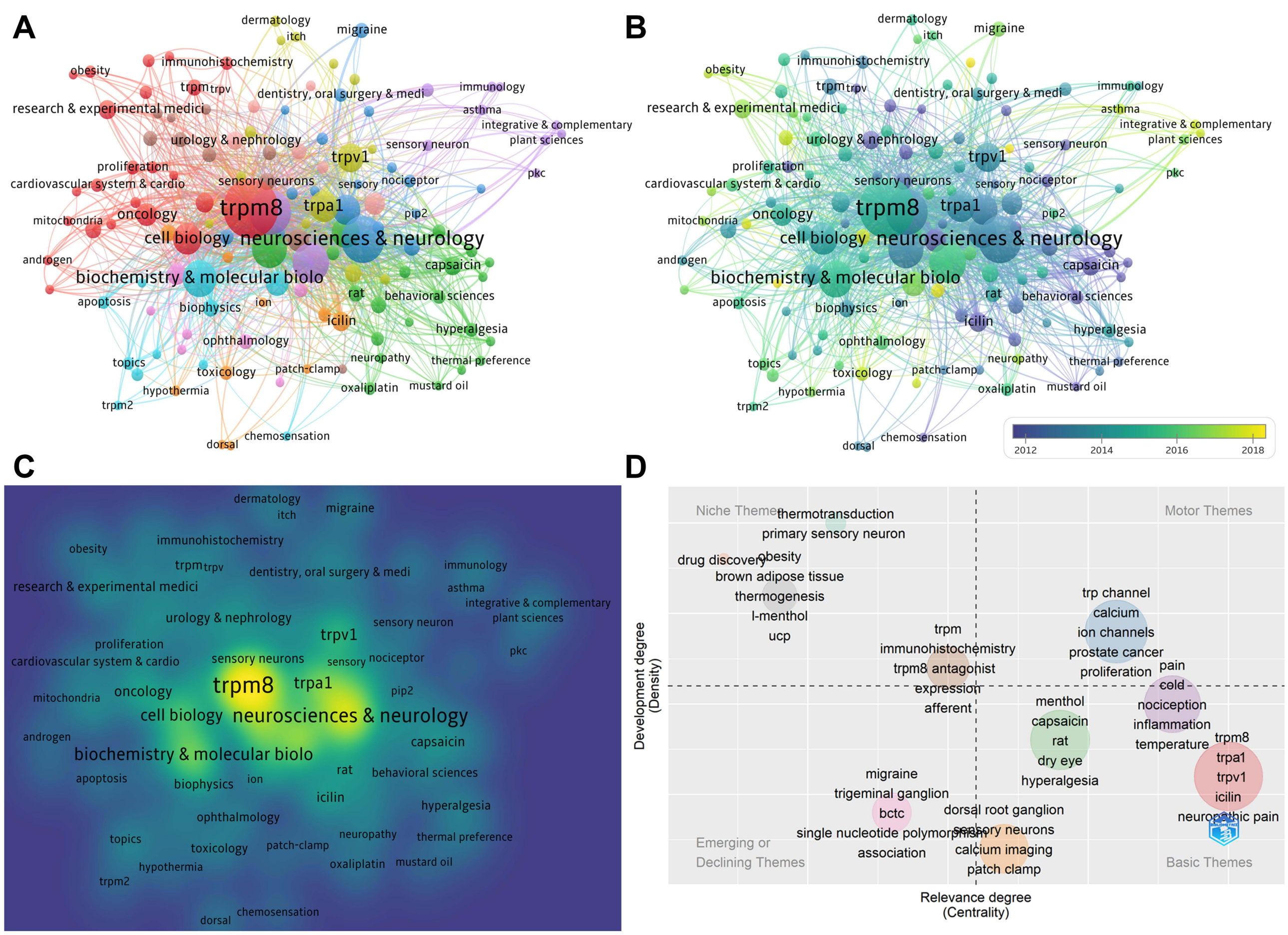

Figure 8 Trends and hotspots of author keywords. (**A**) Co-occurrence network of author keywords with clusters. (**B**) Network of author keywords according to the average publication year. (**C**) Author keywords density map according to the frequency of occurrences (yellow indicated the highest frequency). (**D**) Thematic map of author keywords clusters (bubble size: the occurrences of author keywords in cluster) with four fields: Emerging or declining themes; Niche themes; Basic themes; Motor themes. Different clusters use the five most common author keywords as cluster labels.

The VOSviewer was employed to analyze the co-occurrence of author keywords from TRPM8-related articles. A total of 132 author keywords (occurred 5 times or more) were selected from 2195 author keywords and presented in the form of cluster networks, average published year networks, and density visualized map (Figure 8A–C). Among the 132 author keywords, the top 10 keywords with the most frequent occurrences were TRPM8 (353 times), Neurosciences & Neurology (206 times), TRP channel (185 times), Pharmacology & Pharmacy (136 times), menthol (126 times), Biochemistry & Molecular Biology (115 times), Cell Biology (79 times), TRPA1 (79 times), pain (75 times) and Physiology (75 times) (Table S5). The top 10 author keywords with the most co-occurrences were TRPM8 (total link strength, 1159), Neurosciences & Neurology (675), TRP channel (618), menthol (493), Pharmacology & Pharmacy (395), Biochemistry & Molecular Biology (375), TRPA1 (347), pain (310), transient receptor potential vanilloid 1 (TRPV1) (271) and Cell Biology (256) (Table S5). In addition, a thematic analysis was performed to point out the hotspots among the author keywords (Figure 8D). The thematic map has two types of measurements: centrality (relevance degree) and density (development degree), with four quadrants, "emerging or descending", "highly developed and isolated", "motor themes", and "basic and lateral".[31] Notably, two clusters related to the TRP channel, calcium, prostate cancer, proliferation, pain, cold, nociception, and inflammation were positioned in the motor themes field (Figure 8D).

Discussion

Bibliometric analysis, an important tool to quantify and assess academic publications, has recently been widely used in various research fields.[24] In our study, we retrieved articles from the WoS database in the field of TRPM8 research from 2002 to 2021. And their basic information about describing the current pattern of TRPM8 research through bibliometric analysis was presented with network visualization. The number of publications on TRPM8 research increased rapidly from 2002 to 2014. The trend may be relevant to many researchers in this field across different disciplines (Prevarskaya N., Viana F., de Petrocellis L., etc.) and can be regarded as the initial and golden period of TRPM8 research. Since 2014, the number of published articles every year has remained at a high level, indicating that TRPM8 is still widely concerned, but the number of scholars or projects researching TRPM8 has not greatly increased. Therefore, future research on TRPM8 should cooperate with new scholars from different disciplines and research fields to expand the importance of TRPM8 in other various research fields. The average number of article citations has decreased year by year since 2002. On the one hand, considering the relationship between the length of time that an article was published and the number of citations of an article, it is normal for the number of citations to decline in recent years.[32] On the other hand, since the discovery of TRPM8, the number of landmark scientific discoveries in this research area is relatively small, and it still needs time and unremitting efforts of scholars.

From the perspective of national distribution, the USA is currently the global research leader of TRPM8 with an absolute advantage in scientific production. It has the most publications, citations, and related institutions. Notably, the analysis shows that the USA has active academic collaboration with many countries, such as China and Japan. In addition, the number of scientific productions in Japan, China, Germany, and England has also increased substantially over the past two decades. China ranks third among the countries of correspondents and sixth among the total citations. Most of the research institutions related to the articles are located in the USA, followed by Japan and China. Interestingly, Universidad Miguel Hernández in Spain is the third-most-published institution and has the most institutional collaborations, which may be attributed to the unremitting efforts of Viana F., the third-most-published author. Viana F.'s research mainly focuses on the role of TRPM8 in neurons, tumors, cornea, and other cells, as well as in corneal sensation, obesity, and pharmacology.[33–37] Currently, the global collaboration trend of academic institutions is characterized by small groups, and global cooperation still needs to be strengthened. Nevertheless, several medium research groups have played important roles in the TRPM8 field. Some academic groups and hospitals in Italy and Switzerland have collaborated to demonstrate the potential adjunctive effect of TRPM8 in prostate cancer treatment.[12] Similarly, multiple groups from Turkey, Germany, and Hungary have explored the role of TRPM8 in breast and prostate cancer cell lines together.[38]

The articles related to the TRPM8 research field are mainly published in neurological journals, such as the Journal of Neuroscience, which ranks first in terms of publication volume. Journal co-citation analysis shows that the research about neurology and pharmacology have a strong co-citation trend, suggesting that the current research on TRPM8 is primarily focused on neurons and drugs. Prevarskaya N. from Université Lille 1, France, has published the most articles and has the most collaborations with other scholars. The articles of Prevarskaya N. mainly involve the molecular mechanism of TRPM8 in epidermal homeostasis, prostate cancer, and germ cell cold shock.[39–41] In the author citation analysis, the articles from Nobel laureate Patapoutian A. were mostly cited. Besides, his two articles were published in Cell in 2002 and 2003, which ranked first in both local citations and global citations. This is mainly due to Patapoutian A. 's pioneering discovery that the TRPM8 is the body's cold sensory receptor.[28,29] Over the past two decades, Patapoutian A. has further studied the molecular mechanism of TRPM8 activation and its interaction with other TRP channels.[42–44]

The network maps of author keywords co-occurrence, clustered by subject field or published date, represent the current hotspots and future directions of TRPM8 research. Co-occurrence networks demonstrate that TRPM8 research mainly involves the disciplines of Neurosciences and Neurology, Pharmacology, and Pharmacy, as well as Biochemistry and Molecular Biology. Furthermore, the hotspots of TRPM8 research are involved in multiple cell types (such as neurons, endothelial cells, tumor cells), physiological processes (such as cold sensation, pain, proliferation, metabolism), related ion channels (such as TRPV1, TRPA1) and diseases (such as cancer, migraine, dry eye). TRPM8 is known to be involved in cold allodynia following nerve injury or inflammation. Several studies strongly show that there is a correlation between TRPM8 and migraine.[22,45] A study has reported that the activation of meningeal TRPM8 could induce migraine pain in preclinical rodent model,[45] but another study has mentioned that the activation of meningeal TRPM8 could relieve the inflammatory mediators-induced migraine-like symptoms in mice.[22] These opposite effects may be explained by the different pathogenesis, however, TRPM8 is regarded as a potential new target for migraine treatment whether in neuropathic migraine or inflammation-induced migraine. Associated with cold sensation and nociceptive sensation, TRPM8 has been reported as a potential therapeutic target for dry eye disease. The activation of TRPM8 causes corneal cold sensation and affects dryness and wetness perception, the inhibition of TRPM8 could reduce the neural excitation produced by drying of the cornea in rat.[46] Furthermore, TRPM8 has been indicated to be involved in cell migration and tumor progression.[47,48] Numerous articles have shown that the expression of TRPM8 is upregulated in different tumors such as prostate, pancreatic, colon, and skin cancers.[21] In some cases, TRPM8 can influence tumor aggressiveness and act as a suppressor in the advanced stage of tumor metastasis.[21] The overexpression of TRPM8 reduces the protein level of cyclin-dependent kinase (CDK) 4 and CDK6 to arrest the cell cycle at the G_0/G_1 stage and reduces the level of focal adhesion kinase (FAK) to suppress the migration in prostate cancer cell line.[49] Thus, TRPM8 is also an ideal target for tumor therapy. Furthermore, a gene database analysis of patients with irritable bowel syndrome (IBS) has found that TRPM8 is highly associated with IBS-C and IBS-M.[50] STW 5 and Menthacarin, two herbal drug combinations used for the treatment of visceral hypersensitivity in patients, have the effect to induce the desensitization of TRP channels in primary sensory neurons, peritoneal macrophages, and colonic organoids.[51,52] In addition, previous studies have also shown that TRPM8 agonists can ameliorate intestinal inflammation and reduce the protein levels of several inflammatory factors, such as tumor necrosis factor (TNF) -α, interleukin (IL) −1β, IL-6 and IL-12.[53] The knockout of TRPM8 aggravates the progression of colitis in mice model.[9] In recent years, research on TRPM8 has mainly focused on the nervous system. However, recent work has also found that TRPM8 also plays a crucial role in tumors and the immune system. Therefore, TRPM8 can be regarded as a potential therapeutic target in various diseases and utilized for the development of clinical drugs in the future.

Limitations

The bibliometric analysis exists some limitations. All publications were only collected from the WoS database, no other databases were mentioned. This may cause articles from some other databases to be missed. However, the WoS database is the most frequently used database in scientometrics and includes global high-quality articles. Therefore, our study illustrates the current research trends in TRPM8 to the greatest extent possible. Furthermore, we only analyzed articles in English, possibly ignoring some valuable articles in other languages. Nevertheless, in our literature search without any language restrictions, there were only 4 articles in other languages. If these 4 studies are included, it will lead to the conflict of author keywords in different languages. In addition, the presence of singular and plural, abbreviations, and full names of some author keywords may reduce the accuracy of bibliometric analysis. For this limitation, we have incorporated some major singular and plural, abbreviations and full names of author keywords, such as TRPM8, TRPA1, TRPV1, dorsal root ganglion, sensory neurons, etc. Finally, selection bias may arise in literature screening.

Conclusion

We searched and analyzed 1035 articles in the TRPM8 research area from 2002 to 2021. Despite some limitations, our study shows that the number of TRPM8 research has increased over the past two decades. The USA has an advantage in this field, followed by Japan and China. The most popular disciplines are Neuroscience and Neurology, Pharmacology and Pharmacy, as well as Biochemistry and Molecular Biology. The hotspots in TRPM8 research mainly focus on its effect on pain, cold sensation, and prostate cancer. The global research trends are the activation mechanism of TRPM8 in neurons, the role of TRPM8 in neuronal and non-neuronal diseases, and therapeutic target research.

Abbreviations

TRP, transient receptor potential; TRPM8, transient receptor potential melastatin 8; WoS, Web of Science; SCI-EXPANDED, Science Citation Index Expanded; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; CDK, cyclin dependent kinase; FAK, focal adhesion kinase; IBS, irritable bowel syndrome; TNF, tumor necrosis factor; IL, interleukin.

Data Sharing Statement

Raw data supporting this publication is available from the Web of Science at located at www.webofknowledge.com or by contacting the authors.

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Disclosure

The authors report no conflicts of interest in this work.

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