

The past and future of transient receptor potential

A scientometric analysis

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Abstract

Background: Thermoreceptors include TRPV1 and TRPM8. TRPV1 and TRPM8 are TRP channels. TRP ion channels are widely expressed in many different tissues and cell types, and are involved in different physiological processes. Research on the structure and basic physiological functions of TRPV1 is relatively perfect, and the relationship between the pathogenesis of other members of the TRP family and specific diseases and TRPV1 remains to be explored in depth.

Methods: Articles regarding TRP were culled from the Web of Science Core Collection, and knowledge maps were generated using the CiteSpace software.

Results: In total, 19,862 articles were included. The number of published articles on this topic has rapidly increased since 2000, with more than 1000 articles published per year by 2020. MAKOTO TOMINAGA was the author with the most articles. The countries with the most articles were the United States and China. However, the number of articles in the U.S. was 3 times that in China. The organizations that publish the most articles are Harvard University in the US and Seoul Natl University in South Korea. TRP and the pathogenesis of diseases, such as neuropathy and stroke, are hotspots of current research.

Conclusion: To our knowledge, this is the first study to provide an overview of the literature on TRP. Research on TRPs is developing rapidly.

Abbreviations: TRP = transient receptor potential.

Keywords: bibliometrics, CiteSpace, hotspots, transient receptor potential, trends

1. Introduction

Transient receptor potential (TRP) channels are the vanguard of sensory systems in response to temperature, touch, pain, osmolarity, pheromones, taste, and other stimuli. TRP is expressed at the end of a specific sensory element in the skin.^[1,2] After the skin is stimulated by cold and heat, it activates the TRP protein family. TRPV3 is a subtype protein that senses heat, and TRPM8 is a “cold sense” protein.^[3] Since it was reported in 2005, TRP has attracted considerable interest, and in light of recent events in the Nobel Prize in Physiology or Medicine, more people have followed TRP. Recent evidence suggests that David Julius exploited cryoelectron microscopy (cryo-EM) to visualize conformational transitions of the capsaicin receptor, TRPV1. It describes the conformational transition of TRPV1 and reveals the ion passage of this capsaicin receptor upon stimulation.^[4] Research on TRP involves important diseases in many departments and accounts for the

majority of tumor research. In the future, TRP will become a breakthrough for people to overcome various diseases. However, few writers have been able to draw on any systematic research into TRP. This study systematically reviews the data for TRP, and the knowledge was mapped from the extracted bibliographic records using CiteSpace to analyze the TRP research status, aiming to provide research directions in this field and prospects for future research hotspots. This is the first study to undertake a longitudinal analysis of TRP. The reader should bear in mind that the study is based on Bibliometrics Visualization Analysis.

2. Methods

Literature was extracted from the Web of Science Core Collection, and the search and download process were carried out on October 6, 2021, to eliminate substantial errors

NJ, CP, SZ, and BC contributed equally to this work.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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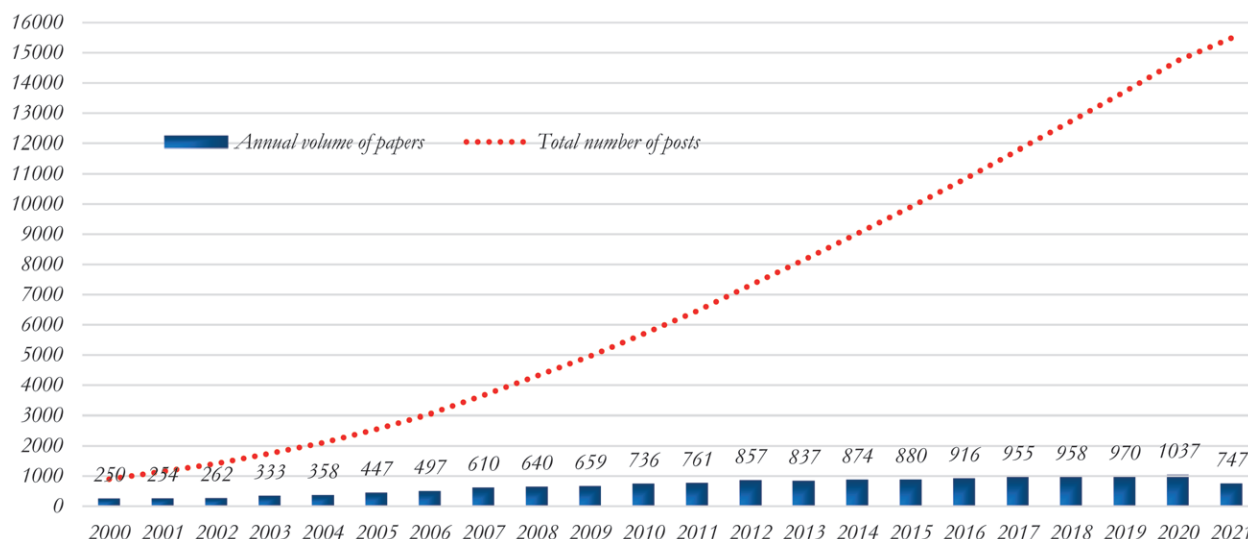


Figure 1. The number of articles published annually of annual articles related to TRP have been steadily increasing from 2000 to 2021. TRP = transient receptor potential.

caused by daily database updates. The search terms were as follows: TS = (“Transient Receptor Potential” OR “TRP”) and invalid documents were eliminated. The search period ranged from June 5, 2001 to June 5, 2021, resulting in 19,862 records fetched. The retrieved papers were exported and saved as plain text files and stored in download_txt format. Given that the data were directly downloaded from the database, ethical approval was not required, and Microsoft Office Excel 2019 and CiteSpace were used to analyze the articles. Analyze the distribution of countries visually, authors and co-cited authors, co-cited references, keyword cluster analysis, and timelines.

3. Results

3.1. Publication outputs

In total, 19,862 articles were examined in the present study. Figure 1 shows the chronological distribution of the publications from 2000 to 2021. As shown in the diagram, the number of articles steadily increased. The histogram represents the number of articles published per year, and the red dotted line represents the cumulative number of articles published. The were of articles in 2020 has reached 1037. As of the search date, there are already 747 articles in 2021, and it is expected that the number of articles published this year will exceed 1500.

3.2. Funding agency

To a certain extent, funding agencies can reflect the hotspots in this field. The more funding there is, the more important is the research field. As shown in Table 1, the top 10 funding agencies include six in the United States and two in Japan, one from the European Union, and one from China. The top two institutions are from the United States, namely the *United States Department of Health Human Services* (5260, 26.483%) and *National Institutes of Health NIH USA* (5243, 26.397%). The third is an institution from China, the *National Natural Science Foundation of China NSFC* (1482, 7.461%).

Table 1

Funding agency of relevant papers on TRP published from 1990 to 2021.

| No. | Funding agency | Record | % of 19,862 |
|-----|--|--------|-------------|
| 1 | United States Department of Health Human Services | 5260 | 26.483 |
| 2 | National Institutes of Health NIH USA | 5243 | 26.397 |
| 3 | National Natural Science Foundation of China NSFC | 1482 | 7.461 |
| 4 | European Commission | 1398 | 7.039 |
| 5 | NIH National Heart Lung Blood Institute NHLBI | 1255 | 6.319 |
| 6 | NIH National Institute of Neurological Disorders Stroke NINDS | 1222 | 6.152 |
| 7 | Ministry of Education Culture Sports Science And Technology Japan MEXT | 969 | 4.879 |
| 8 | NIH National Institute of Diabetes Digestive Kidney Diseases NIDDK | 804 | 4.048 |
| 9 | Japan Society for the Promotion Of Science | 789 | 3.972 |
| 10 | NIH National Institute of General Medical Sciences NIGMS | 719 | 3.62 |

TRP = transient receptor potential.

3.3. Analysis of authors and author collaboration

In total, 14,44 author were chosen/selected from 19,862 publications. The top 10 most productive authors contributed 619 articles (3.12%) to the TRP research (Table 2). MAKOTO TOMINAGA contributed the most articles (113 articles), followed by YASUO MORI and LUTZ BIRNBAUMER with 38 and 37 publications, respectively (Table 3). Their centrality scores were low, with only one researcher reaching above 0.05. The co-citation network map of the authors contained 1741 links, and there was active collaboration among the productive authors (Fig. 2).

3.4. Distribution of countries/regions and institutions

From 415 countries and 841 units, 19,862 papers were published. As shown in Table 3, the most significant number of

Table 2

Top 10 authors in the number of papers published.

| No. | Freq | Degree | Centrality | Author | Year | Half-life |
|-----|------|--------|------------|------------------------|------|-----------|
| 1 | 113 | 25 | 0.03 | MAKOTO TOMINAGA | 2006 | 8.5 |
| 2 | 78 | 27 | 0.04 | YASUO MORI | 2006 | 8.5 |
| 3 | 77 | 16 | 0.06 | LUTZ BIRNBAUMER | 2007 | 6.5 |
| 4 | 63 | 13 | 0.02 | VINCENZO DI MARZO | 2007 | 5.5 |
| 5 | 60 | 10 | 0.02 | INSUK SO | 2007 | 5.5 |
| 6 | 59 | 20 | 0.04 | BERND NILIUS | 2007 | 2.5 |
| 7 | 53 | 13 | 0.03 | THOMAS VOETS | 2007 | 6.5 |
| 8 | 39 | 6 | 0 | LUCIANO DE PETROCELLIS | 2007 | 5.5 |
| 9 | 39 | 9 | 0.04 | WOLFGANG LIEDTKE | 2007 | 3.5 |
| 10 | 38 | 15 | 0.03 | THOMAS GUDERMANN | 2008 | 6.5 |

Table 3

Top 10 countries/regions and institutions related to pyroptosis.

| No. | Country | Year | Centrality | Count (%) | Institution | Year | Centrality | Count (%) |
|-----|-------------|------|------------|--------------|------------------------|------|------------|------------|
| 1 | USA | 1990 | 1.3 | 6386 (32.15) | Harvard Univ | 1999 | 0.07 | 226 (1.14) |
| 2 | China | 2003 | 0.02 | 2165 (10.90) | Seoul Natl Univ | 2003 | 0.02 | 216 (1.09) |
| 3 | Japan | 2003 | 0.04 | 1377 (6.93) | Johns Hopkins Univ | 1999 | 0.07 | 191 (0.96) |
| 4 | Germany | 2003 | 0.06 | 1150 (5.79) | Duke Univ | 1998 | 0.04 | 188 (0.95) |
| 5 | England | 2004 | 0.07 | 745 (3.75) | Kyoto Univ | 1998 | 0.04 | 182 (0.92) |
| 6 | South Korea | 2003 | 0.03 | 566 (2.85) | Univ Maryland | 1998 | 0.04 | 181 (0.91) |
| 7 | Italy | 2005 | 0.03 | 544 (2.74) | Katholieke Univ Leuven | 2001 | 0.05 | 165 (0.83) |
| 8 | Canada | 2007 | 0.03 | 519 (2.61) | Chinese Acad Sci | 2005 | 0.01 | 134 (0.67) |
| 9 | Japan | 1990 | 0.13 | 488 (2.46) | CNR | 1998 | 0.03 | 125 (0.63) |
| 10 | Germany | 1991 | 0.19 | 486 (2.45) | Univ Cambridge | 1998 | 0.03 | 118 (0.59) |

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 Selection Criteria: p-index (k=25), LRF=3.0, UN=10, LBY=5, e=1.0
 Network: N=1444, E=1741 (Density=0.0017)
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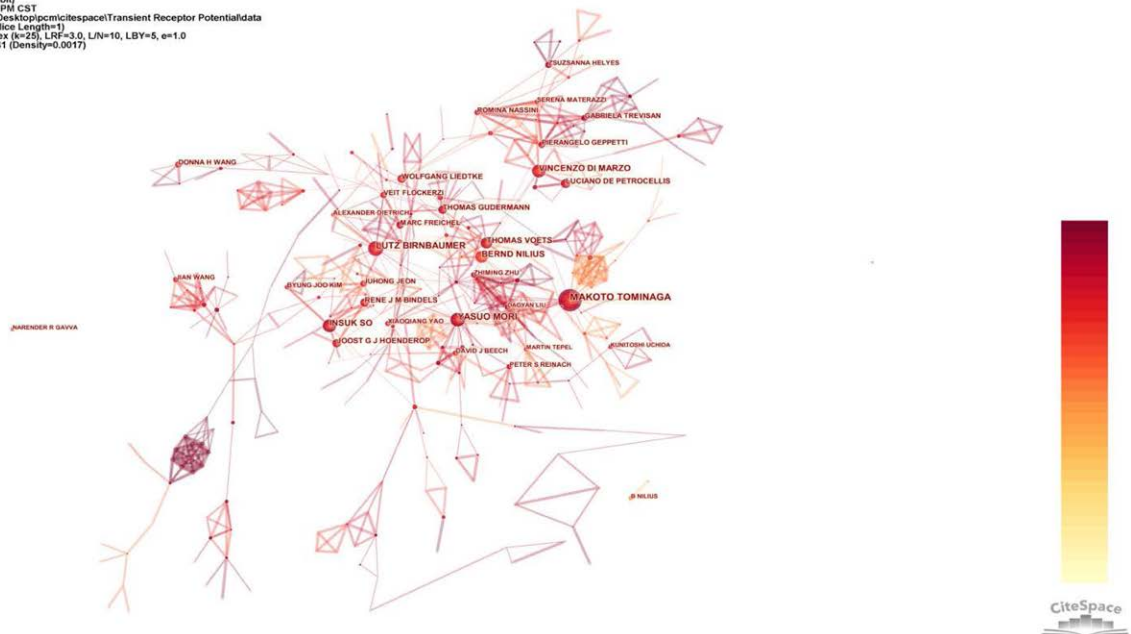


Figure 2. Map of authors' collaborations related to TRP research. TRP = transient receptor potential.

publications came from the USA (6386, 32.15%), which is far more than 3 times higher than that of China (2165, 10.90%). Other countries that published more than 1000 articles included Japan (1377, 6.93%) and Germany (1150, 5.79%). Among the top 3 institutions, 2 of institutions are found to be in the USA: Harvard University and Johns Hopkins University. The

second-ranked institution is Seoul National University of South Korea, as indicated by the purple circles in Figures 3 and 4. Each circle in the figure represents a country, and the size of the circle indicates the country's publication output. The lines between the circles denote cooperation between countries; the wider the lines, the closer the cooperation.

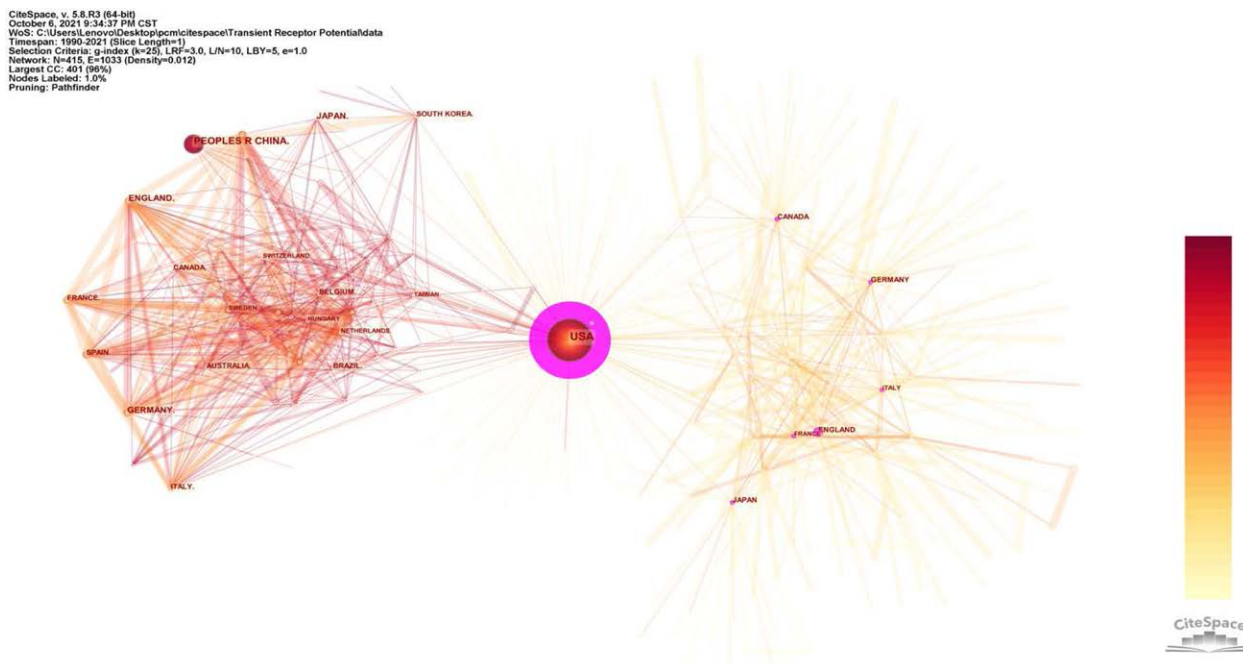


Figure 3. Distribution of publications from different countries/regions.

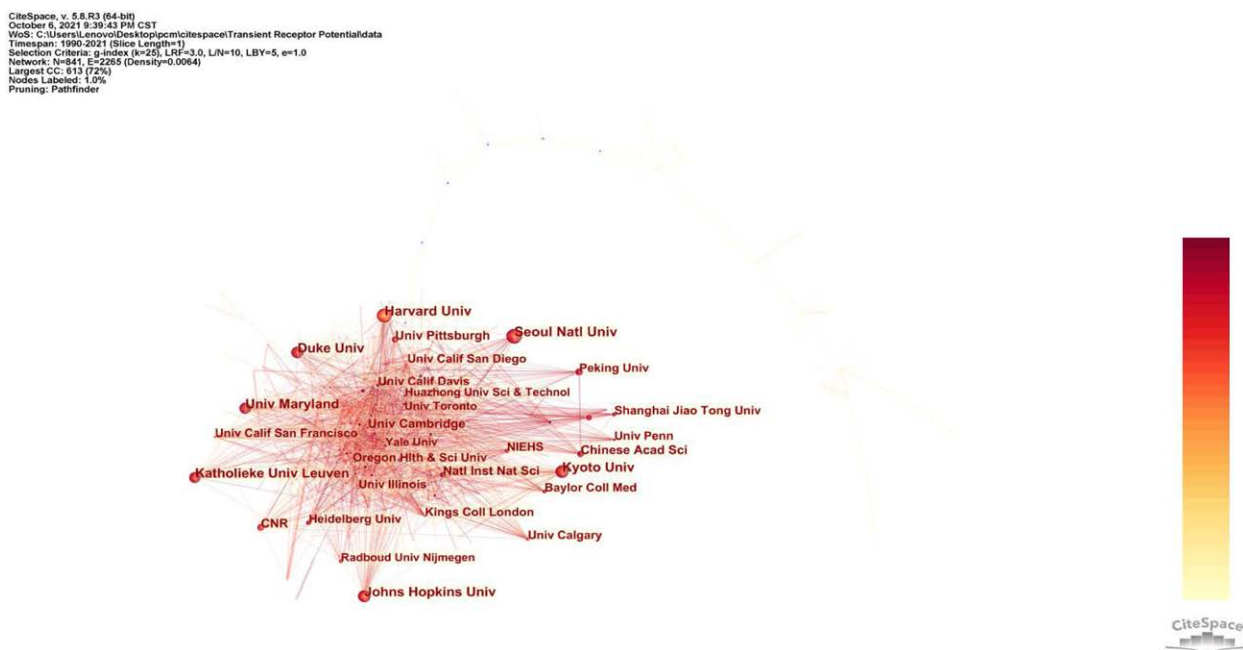


Figure 4. Distribution of publications from different institutions.

3.5. Co-occurrence of keywords and analysis of research hotspots

Keywords were extracted from titles and abstracts of all 19,862 publications. Figure 5 shows the keywords mentioned most frequently in publications; there were 1126 nodes and 7864 links in the network map. In terms of frequency, these terms “activation”(2973 times), “expression”(2518 times), “receptor”(1962 times), “channel”(1702 times), “ion channel”(1264 times), “rat”(1237

times), “mechanism”(1192 times), “cell”(1189 times), “pain”(1094 times), “protein”(976 times) appeared most. The top 20 keywords in terms of their frequency of use are listed in Table 4. By analyzing the evolution trend of keywords over time, one can better understand the dynamic trend of the TRP research field. For the documents selected in the WOS database, keywords were used to analyze the years. Documents with a node of 1126 and a line of 7864 were drawn as keyword co-occurrence time zone diagrams, as shown in Figure 6. We found that the initial research

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 Nodes Labeled: 1.0%
 Pruning: Pathfinder

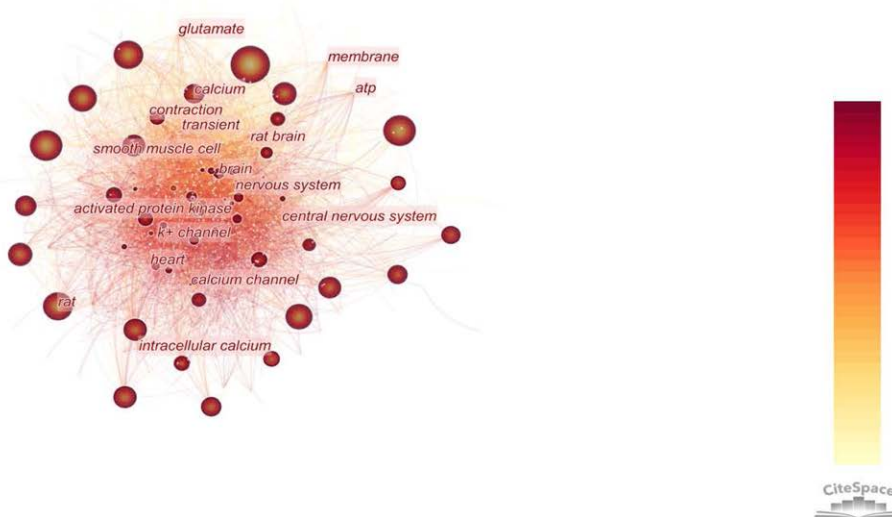


Figure 5. Map of co-occurring keywords related to TRP research. TRP = transient receptor potential.

Table 4
 Top 20 keywords related to TRP.

| No. | Freq | Degree | Centrality | Keyword | No. | Freq | Degree | Centrality | Keyword |
|-----|------|--------|------------|-------------|-----|------|--------|------------|--------------------|
| 1 | 2973 | 43 | 0.02 | activation | 11 | 969 | 32 | 0.01 | capsaicin receptor |
| 2 | 2518 | 36 | 0.02 | expression | 12 | 795 | 45 | 0.02 | inhibition |
| 3 | 1962 | 33 | 0.01 | receptor | 13 | 785 | 37 | 0.01 | neuron |
| 4 | 1702 | 41 | 0.01 | channel | 14 | 767 | 53 | 0.03 | calcium |
| 5 | 1264 | 33 | 0.01 | ion channel | 15 | 689 | 34 | 0.01 | cation channel |
| 6 | 1237 | 52 | 0.03 | rat | 16 | 630 | 41 | 0.02 | mice |
| 7 | 1192 | 42 | 0.01 | mechanism | 17 | 622 | 30 | 0.01 | in vitro |
| 8 | 1189 | 30 | 0.01 | cell | 18 | 567 | 36 | 0.01 | release |
| 9 | 1094 | 26 | 0 | pain | 19 | 566 | 43 | 0.02 | sensory neuron |
| 10 | 976 | 37 | 0.01 | protein | 20 | 532 | 38 | 0.02 | identification |

TRP = transient receptor potential.

focused on channels, activation, acetylcholine, etc. The keywords that appeared in the second stage were cgrp and hypertrophy.

A clustering analysis of the keywords was performed. The results are presented in Figure 7 and Table 5. There were 8 clusters of keywords, which are #0“breast cancer cell,” #1“ventricular myocyte,” #2“sensory neuron,” #3“store-operated channel,” #4“hippocampal slice,” #5“cerebral ischemia-reperfusion cell,” #6“design synthesis,” #7“adrenergic receptor”.

Keywords with strong burst strength are another important indicator to reflect research hotspots, frontiers, and emerging trends over time. There are 553 hot keywords from 1990 to 2021 (附件 S1). For the focus and hotspot of research in this field, we display the keywords in 3 parts. As shown in Table 6, The top 10 keywords with the longest research time in the past 30 years are displayed. As shown in Table 7, The top 15 keywords from 2015 to 2021 are displayed. Table 8 displays 25 keywords from 2019 to 2021. Most notably, 25 keywords have continued to 2021, and the bursts are still ongoing, indicating that these research directions have received great attention in recent years and have the potential to become new research hotspots in the future.

3.6. Co-citation of reference

The top 20 TRP articles with the highest citations are shown in Table 9 and Figure 8. The authors of these papers are Clapham,^[5] Nilius et al,^[6] Bautista et al,^[7] Venkatachalam and Montell,^[8] Ramsey et al,^[9] Kwan et al,^[10] Liao et al,^[11] Clapham et al,^[12] Jordt et al,^[13] Story et al,^[14] Bandell et al,^[15] Macpherson et al,^[16] Montell et al,^[17] Cao et al,^[18] Julius,^[19] Paulsen et al,^[20] Montell,^[21] Gao et al,^[22] McNamara et al,^[23] and Moran et al.^[24] Among the first 20 articles, there were 4 reviews^[8,9,23,24] and 16 original articles. These articles provide foundational research on TRP, including the discovery of TRP channels, the structure of related proteins, and their correlation with diseases.

4. Conclusion

This study used scientometric tools to identify the knowledge base and research hotspots of TRPs. The number of published articles on this topic has rapidly increased since 2000, with more than 1000 articles published per year by 2020. The top 3 funded projects are the United States Department of Health Human Services, National Institutes of Health NIH USA, and National Natural Science Foundation of China NSFC.

Table 5
Top 8 subjects of cluster analysis.

| Cluster ID | Size | Year | Cluster label (LLR) |
|------------|------|------|--|
| #0 | 210 | 2004 | transient receptor; calcium-sensing receptor; risk factors; interleukin-1 receptor antagonist; cxcl12lexpression; proliferation; ion channel; cancer; pathway |
| #1 | 184 | 1997 | transient receptor; potential channels; heart failure; trpc channels; potential canonical channelsactivation; channel; mechanism; in vivo; involvement |
| #2 | 184 | 2008 | transient receptor; potential vanilloid type; chemokine receptor; renal injury; deoxycorticosterone acetate-saltpain; expression; neuron; thermosensation; nociceptor |
| #3 | 184 | 2003 | transient receptor; endothelial barrier dysfunction; tumor necrosis factor-alpha; store-operated calcium ion; growthprotein; expression; domain; cloning; period |
| #4 | 180 | 1999 | transient receptor; potential ankyrin; neuron differentiation; social preference; anxiolytic-like behaviorlong term; ischemic penumbra; animal models; uveal melanoma; superior colliculus |
| #5 | 151 | 2012 | transient receptor; potential canonical channel; myocardial infarction; neurotrophic factor; tooth developmentoxidative stress; dopamine d-4 receptor; soce; adp-ribose; ip3r |
| #6 | 22 | 2008 | identification; expression; inflammation; capsaicin receptor; primary afferent neurontransient receptor; potential canonical; non-selective cation channel; artemisia annua; membrane-delimited activator secretion gene therapy; adeno-associated virus; ocular neovascularization; vascular endothelial growth factor; felinelions sodium; ions calcium; opioid morphine; transgenic mouse; myocardial contractility |
| #7 | 9 | 1998 | |

Table 6
Top 10 keywords with the strongest citation bursts from 1990 to 2021.

| Keywords | Year | Strength | Begin | End | 1990–2021 |
|------------------------------|------|----------|-------|------|-----------|
| depolarization | 1990 | 9.53 | 1991 | 2009 | |
| messenger rna | 1990 | 38.23 | 1991 | 2007 | |
| calcium current | 1990 | 12.85 | 1992 | 2008 | |
| dentate gyrus | 1990 | 7.45 | 1993 | 2009 | |
| cloning | 1990 | 34.91 | 1991 | 2006 | |
| transient outward current | 1990 | 27.75 | 1991 | 2006 | |
| d aspartate receptor | 1990 | 15.3 | 1991 | 2006 | |
| transient | 1990 | 15.09 | 1991 | 2006 | |
| potassium current | 1990 | 10.67 | 1992 | 2007 | |
| transient forebrain ischemia | 1990 | 9.33 | 1992 | 2007 | |

Table 7
Top 15 keywords with the strongest citation bursts from 2015 to 2021.

| Keywords | Year | Strength | Begin | End | 1990–2021 |
|-----------------------|------|----------|-------|------|-----------|
| rat model | 1990 | 14.27 | 2015 | 2021 | |
| exposure | 1990 | 11.13 | 2015 | 2021 | |
| pathogenesis | 1990 | 10.54 | 2015 | 2021 | |
| trpv1 channel | 1990 | 10.23 | 2015 | 2021 | |
| food intake | 1990 | 10.23 | 2015 | 2021 | |
| multiple sclerosis | 1990 | 9.44 | 2015 | 2021 | |
| potential vanilloid 1 | 1990 | 8.91 | 2015 | 2021 | |
| behavior | 1990 | 8.21 | 2015 | 2021 | |
| insulin resistance | 1990 | 6.58 | 2015 | 2021 | |
| efficacy | 1990 | 5.91 | 2015 | 2021 | |
| inflammatory response | 1990 | 4.95 | 2015 | 2021 | |
| ischemic stroke | 1990 | 4.73 | 2015 | 2021 | |
| recognition | 1990 | 3.63 | 2015 | 2021 | |
| role | 1990 | 15.11 | 2016 | 2021 | |
| trpa1 | 1990 | 11.98 | 2016 | 2021 | |

research has been conducted on specific diseases, such as chronic pain, neurology, oncology, dermatology, pulmonology, cardiology, urology, and some rare diseases.^[2,5]

This article describes the longitudinal development process of the TRP. With people’s in-depth understanding and research on TRP, it is believed that there will be further breakthroughs in the future, which will bring good news to the pathogenesis, research, and development of new drugs.

Author contributions

All authors have read and approved the manuscript and have ensured that this is the case.

Conceptualization: Nan Jiang, Ciming Pan, Changwu Dong.

Data curation: Ciming Pan.

Investigation: Nan Jiang.

Methodology: Shuhan Zhang, Bin Cheng.

Table 9
(Continued)

| No. | Freq | Degree | Centrality | Author | Year | Source | DOI | Main conclusion |
|-----|------|--------|------------|---------------|------|----------------------|---------------------------------------|---|
| 8 | 148 | 6 | 0 | Clapham DE | 2001 | NAT REV NEUROSCI | 10.1038/35077544 | The channel subunits have six transmembrane domains that most probably assemble into tetramers to form non-selective cationic channels, which allow for the influx of calcium ions into cells. Three subgroups comprise the TRP channel family; the best understood of these mediates responses to painful stimuli. |
| 9 | 147 | 9 | 0.02 | Jordt SE | 2004 | NATURE | 10.1038/nature02282 | These findings identify a cellular and molecular target for the pungent action of mustard oils and support an emerging role for TRP channels as ionotropic cannabinoid receptors. |
| 10 | 145 | 11 | 0.05 | Story GM | 2003 | CELL | 10.1016/S0092-8674(03)00158-2 | The characterization of ANKTM1, a cold-activated channel with a lower activation temperature compared to the cold and menthol receptor, TRPM8. |
| 11 | 142 | 10 | 0.01 | Bandell M | 2004 | NEURON | 10.1016/S0896-6273(04)00150-3 | TRPA1 activation elicits a painful sensation and provide a potential molecular model for why noxious cold can paradoxically be perceived as burning pain. |
| 12 | 141 | 11 | 0.01 | Macpherson LJ | 2007 | NATURE | 10.1038/nature05544 | Covalent modification of reactive cysteines within TRPA1 can cause channel activation, rapidly signaling potential tissue damage through the pain pathway. |
| 13 | 141 | 6 | 0.01 | Montell C | 2002 | CELL | 10.1016/S0092-8674(02)00670-0 | TRP cation channels display an extraordinary assortment of selectivities and activation mechanisms, some of which represent previously unrecognized modes for regulating ion channels. The biological roles of TRP channels appear to be equally diverse and range from roles in pain perception to male aggression. |
| 14 | 129 | 6 | 0.01 | Cao EH | 2013 | NATURE | 10.1038/nature12823 | TRPV1 opening is associated with major structural rearrangements in the outer pore, including the pore helix and selectivity filter, as well as pronounced dilation of a hydrophobic constriction at the lower gate, suggesting a dual gating mechanism. Allosteric coupling between upper and lower gates may account for rich physiological modulation exhibited by TRPV1 and other TRP channels. |
| 15 | 127 | 6 | 0 | Julius D | 2013 | ANNU REV CELL DEV BI | 10.1146/annurev-cellbio-101011-155833 | Nociception is the process whereby primary afferent nerve fibers of the somatosensory system detect noxious stimuli. Three members of the transient receptor potential (TRP) ion channel family--TRPV1, TRPM8, and TRPA1--as molecular detectors of thermal and chemical stimuli that activate sensory neurons to produce acute or persistent pain. |
| 16 | 124 | 9 | 0.02 | Paulsen CE | 2015 | NATURE | 10.1038/nature14367 | The TRPA1 ion channel (also known as the wasabi receptor) is a detector of noxious chemical agents encountered in our environment or produced endogenously during tissue injury or drug metabolism. A blueprint for structure-based design of analgesic and anti-inflammatory agents. |
| 17 | 123 | 1 | 0 | Montell Craig | 2005 | Sci STKE | 10.1126/stke.2722005re3 | The TRP superfamily is divided into 7 subfamilies, the first of which is composed of the "classical" TRPs' (TRPC subfamily). |
| 18 | 116 | 14 | 0.04 | Gao Y | 2016 | NATURE | 10.1038/nature17964 | The locations of annular and regulatory lipids and showed that specific phospholipid interactions enhance binding of a spider toxin to TRPV1 through formation of a tripartite complex. |
| 19 | 112 | 12 | 0.02 | McNamara CR | 2007 | P NATL ACAD SCI USA | 10.1073/pnas.0705924104 | TRPA1 is the principal site of formalin's pain-producing action in vivo, and that activation of this excitatory channel underlies the physiological and behavioral responses associated with this model of pain hypersensitivity. |
| 20 | 111 | 7 | 0.01 | Moran MM | 2011 | NAT REV DRUG DISCOV | 10.1038/nrd3456 | This Review focuses on recent developments in the TRP channel-related field, and highlights potential opportunities for therapeutic intervention. |

TRP = transient receptor potential.

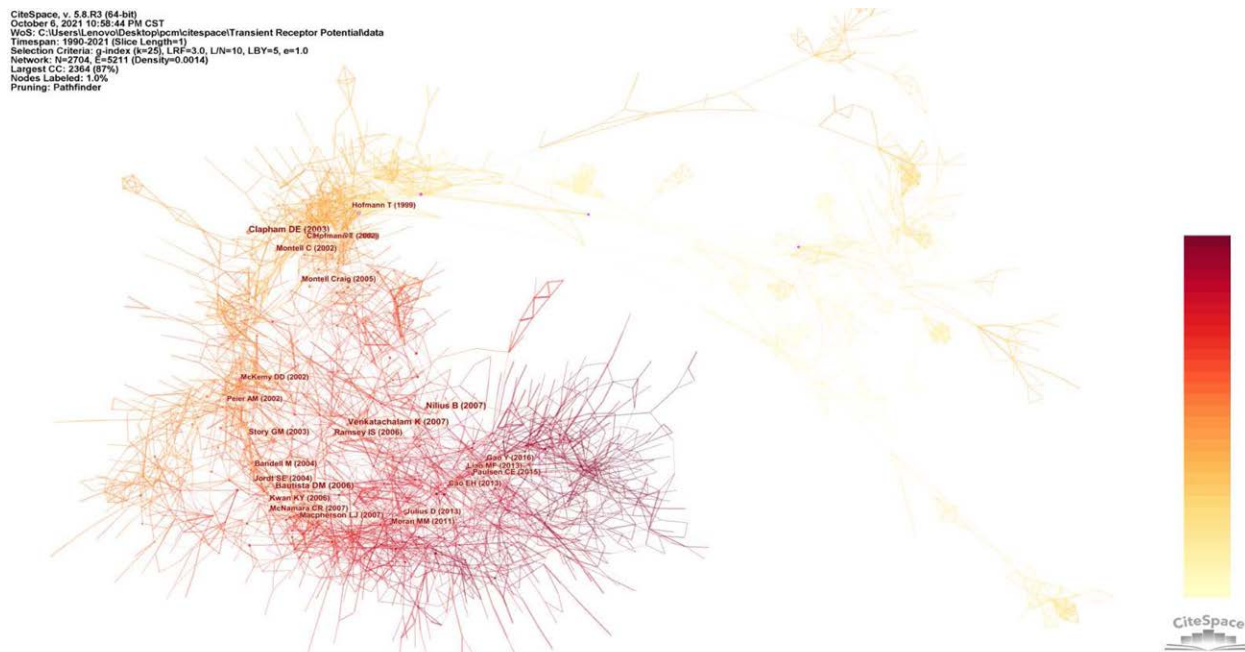


Figure 8. Document co-citation analysis in TRP research. TRP = transient receptor potential.

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[14] Story GM, Peier AJ, Reeve AJ, et al. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell*. 2003;112:819–29.

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