REVIEW ARTICLE

A Global Research Trend on Endolysosomal Calcium Two-Pore Channels via Bibliometric Analysis

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ABSTRACT

Two-pore channel (TPC) is an endolysosomal calcium channel implicated in numerous physiological processes and pathologies. Since no bibliometric studies have been conducted to evaluate the typical characteristics of TPC's research, this study sought to pinpoint TPC's global research trends and hotspots. The Scopus database was searched for TPC-related articles from 2000 to 2022. The data were analysed using Harzing's Publish, Open Refine, and VOS viewer. In total, 292 TPC-related articles written in English were analysed. This study demonstrates that the publication rate of TPC has increased since their discovery in 2000 and will continue to increase until 2022. Over the past 22 years, research on TPC has focused on elucidating its function in calcium signalling, revealing its significance in a variety of physiological and pathological conditions. Yet, there are some research prospects for TPC that are currently understudied and warrant attention, notably in the context of autophagy, cancer, and COVID-19.
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Keywords: Bibliometrics, COVID-19, calcium channels, lysosomes, NAADP

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INTRODUCTION

A group of nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive channels named two-pore channel (TPC) conducts calcium (Ca^{2+}) outflow from intracellular storage. TPC1 and TPC2, the two isoforms of TPC present in humans, are localised to the lysosomes and endosomes, respectively (1). TPC regulates a wide range of cellular activities, including angiogenesis and autophagy (2). Inductions of angiogenesis by vascular endothelial growth factor (VEGF) in melanoma and endothelial cells were strongly suppressed when TPC-mediated Ca^{2+} signalling is impaired (3). Similarly, silencing of TPC1 and TPC2 reduces the viability of cardiomyocytes under stress conditions (4). These suggest TPC's significance in maintaining the proper basal and induced autophagic flow in cardiomyocytes. Additionally, TPC is also linked with various diseases such as Parkinson's disease and cancer (5, 6). Blocking TPC2 activity via pharmacological or gene silencing approaches impedes cancer-related processes like angiogenesis and migration (3). Very recently, TPC has been shown to be a potential target for COVID-19 treatment (7). The virus failed to invade host cells when TPC is silenced genetically or inhibited pharmacologically. Looking at its importance in numerous physiological and pathological conditions, it would be high time to study the overall picture of TPC research via bibliometric approach.

Bibliometric analysis is an effective technique for assessing current trends in scientific research and quantifying a field's development through published literature (8). This technique has been widely employed in many fields to examine research frontiers and hotspots, find worldwide collaborations, and evaluate research output of institutions, countries, and authors. Bibliometric analysis enables consumers to swiftly obtain information about a person's, institution's, or country's scientific output by utilising key metrics such as quantity, impact factor (IF), and citations of published papers over time (9). Large data sets, sometimes numbering in the hundreds or thousands, are employed for bibliometric analyses (8). The use of statistical analyses on the expanding body of available data enables more precise mapping of scientific collaboration, ranks, and advancement (10). Bibliometric analysis offers an unbiased and thorough overview of the scholarly literature pertaining to a particular field of research, serving to demonstrate research patterns and uncover potential future avenues of inquiry. This contrasts with other frequently used review methods, such as systematic reviews, which are confined to particular and constrained facets of a research question. Moreover, bibliometric analysis is straightforward, objective, and unbiased, compared to peer review technique. However,

since bibliometric analysis is a quantitative method, it may exhibit limitations in capturing the qualitative aspects of research, including its overall quality and societal impact.

To date, no bibliometric studies have been reported examining the overall characteristics of research undertaken on TPC. The current study utilised bibliometric techniques to investigate TPC-related publications obtained from the Scopus database. The goal was to present a retrospective and current snapshot of mainstream research on TPC around the world from 2000 through 2022. Specifically, this study aimed to identify the research areas of TPC that have received significant attention from different countries, organisations, and authors.

METHOD

The data search was carried out on August 2, 2022. To prevent any potential deviation from the daily database updating, the obtained data was collected in a single day. The following search terms were entered into the database: "two-pore channel" OR "two-pore segment channel" OR tpcn OR tpc1 OR tpcn1 OR tpc2 OR tpcn2. The data for analysis were retrieved from 2000-2022 from Scopus, a multidisciplinary and selective database with a more expanded coverage of all major disciplines compared to the Web of Science (11, 12). In total, 684 publications were obtained from the search. For analysis, only articles and reviews written in English were included. Prior to data exportation, filtering and screening of the data were performed to remove extraneous data, followed by harmonisation of the data using the Openrefine software. Articles that were not related to TPC were excluded such as articles on thyroid cancer cells, total peripheral conductance and triphenylamine dye. These irrelevant papers were also retrieved from the search due to the presence of the acronym TPC in either their title, abstract or keywords. In the end, only 292 publications that specifically focused on the channel TPC were included in the analysis. The retrieval strategy of the experiments is shown in Fig. 1.

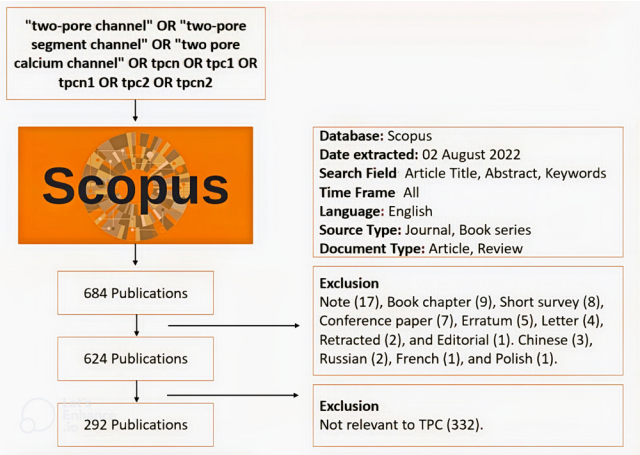

Figure 1: Flow chart of data collection

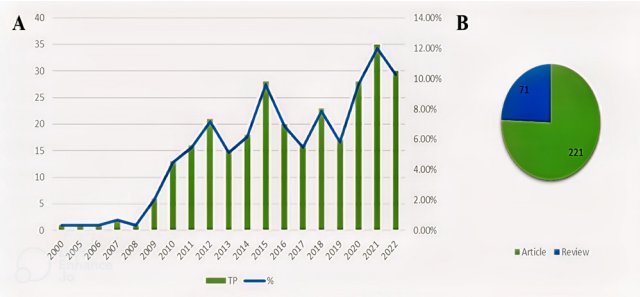

Figure 2: Publication outputs on TPC-related research. (A) Annual publications of TPC, (B) Document type of TPC publication.

RESULTS

Annual publication outputs and document type

Fig. 2A depicts the annual publications on TPC from 2000 until 2022. The earliest publication on TPC was on the cloning of this channel published in 2000. A total of 292 papers were used for the present study. Out of the 292 articles analysed, 221 were research articles, while 71 were review articles (Fig. 2B).

Authors, institutions, and countries contributing to global publications of TPC

Overall, 160 authors from different countries and institutions contributed to the increase in knowledge on TPC. Antony Galione from the University of Oxford, United Kingdom (UK) published the highest number of publications (41) and received the highest co-citations (1514). Sandip Patel of the University College London, UK, came in second with 39 publications and 1298 co-citations. These indicated that both authors are prolific and credible, producing high quality articles that are widely acknowledged by others. Other highly cited authors with more than 700 co-citations were Eugen Brailoiu and Margarida Ruas.

In total, 43 countries and 31 institutions were engaged in TPC research. In accordance with the top authors, the most active country in TPC research was the UK with 112 publications (38.36 %), followed closely by the US with 100 publications (34.25 %). Likewise, the University of Oxford, UK was the most prolific institutions with 77 publications. It was followed by the University of College London, UK, and Ludwig-Maximilians-Universitɑt Mьnchen, Germany, with 40 and 31 publications, respectively.

Distribution of TPC journals

Entirely, 32 journals have published articles on TPC. Cell Calcium (IF = 4.69) has published the highest number of publications on TPC with 28 articles. This is followed Journal of Biological Chemistry (IF = 5.15) with a total of 21 articles. While Proceedings of the National Academy of Sciences of the United States of America (IF = 11.20) was at number three with 9 articles.

Most frequently cited articles

The top 10 highly cited articles on TPC are listed in Table I. The total citations received by these articles ranged from 205 to 1668. Out of the 10 articles listed, seven were original articles while the remaining three were review articles. Three quarters of the articles were published in journals with an IF above 10. The paper by Xiuyuan Ou in 2020 received the highest citation with 1668 total citations. This paper was published in Nature Communication (IF = 14.91) and discussed the role of TPC2 in SARS-CoV-2 entrance. The article by Calcraft in 2009 came second in the list. It was published in Nature (IF = 49.962) and received 563 citations. It is one of the earliest communications that highlighted the mobilisation of calcium via TPC2 following NAADP stimulation. Meanwhile, at number three was a review by Xu in 2015 with 542 citations. This review discussed the role of TPC in lysosomal physiology and was published in Annual physiology review (IF = 19.318).

Hotspots of studies on TPC

Keywords indicate the principal content of a research. Using VOSviewer 1.6.18, the keyword co-occurrence can be analysed to present the research hotspots in clear visual outputs. All 292 publications' titles and abstracts were mined for 95 keywords. The findings suggested that research on TPC mostly concerned with the role of TPC in endolysosomal (EL) calcium signalling, autophagy, and cancer.

To examine the keywords deeper, a network visualisation map of author keywords was produced using VOSviewer (Fig. 3A). Each circle or node represents a keyword, and each directed edge represents a link between one keyword with another. The minimum number of occurrences per keyword was 3. Keywords that were commonly listed together were represented in the same colour and grouped in one cluster. Hence, five clusters of author keywords were formed. Keywords in the red

Table I: Ten top highly cited papers in TPC research

Title	First author	Journal (IF2021)	Year	Total Citation	Main conclusion
Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV	Xiuyuan Ou	Nature communication (14.91)	2020	1668	The authors presented that the SARS-CoV-2 receptor is human angiotensin-converting enzyme 2. Importantly, PIKfyve, TPC2, and cathepsin L are necessary for SARS-CoV-2 entrance.
NAADP mobilizes calcium from acidic organelles through two-pore channels	Peter J. Calcraft	Nature (49.962)	2009	563	According to the authors, TPC2, a lysosomal two-pore channel, is the molecular target of NAADP. TPCs are activated by NAADP to release Ca^{2+} from acidic organelles and induce more Ca^{2+} signals.
Lysosomal physiology	Haoxing Xu	Annual physiology review (19.318)	2015	542	The author summarized that TRPML and TPCs are lysosomal channels that govern lysosomal ion homeostasis, membrane potential, catabolite export, membrane trafficking, and nutrient sensing via mediating ion flux across peripheral membranes.
TPC proteins are phosphoinositide-activated sodium-selective ion channels in endosomes and lysosomes	Xiang Wang	Cell (41.582)	2012	349	The authors' findings show that, in contrast to the earlier hypothesis, TPCs are sodium-selective channels that are activated by PI (3, 5) P2 rather than NAADP.
Two pore channels control Ebolavirus host cell entry and are drug targets for disease treatment	Yasuteru Sakurai,	Science (47.7)	2015	344	This study discovered that the endosomal calcium channels known as TPCs are necessary for Ebolavirus entrance into host cells. Trafficking of viruses was stopped, and infection was avoided by inhibiting TPC function.
Two newly identified genetic determinants of pigmentation in Europeans	Patrick Sulem	Nature Genetics (38.3)	2008	269	The authors discussed the findings of a genome-wide association research for polymorphisms linked to human pigmentation. It demonstrated that two TPCN2 coding variants are linked to hair color, and a variant linked to skin sensitivity to sunlight, freckling, and red hair.
Molecular mechanisms of endolysosomal Ca^{2+} signalling in health and disease	Anthony J. Morgan	Biochemical (3.8)	2011	267	The authors of this review concentrated on the physiology of the NAADP and the TPCs. It showed that NAADP-gated TPCs control a variety of cellular activities and contribute to illness.
Molecular genetics of human pigmentation diversity	Richard A. Sturm	Human Molecular Genetics (6.1)	2009	265	The author investigated the molecular genetics of the diversity in human pigmentation. A number of genome-wide association studies for pigmentation have been carried out and single nucleotide polymorphism markers including SLC24A4, IRF4, and TPCN2 have been discovered.
MTOR regulates lysosomal ATP-sensitive two-pore Na^{+} channels to adapt to metabolic state	Chunlei Cang	Cell (41.582)	2013	253	The authors indicated that TPCs are a novel ion channel family that connects a cell's metabolic state to endolysosomal function and is important for physical endurance under dietary restriction.
The two-pore channel TPCN2 mediates NAADP-dependent Ca^{2+}-release from lysosomal stores	Xiangang Zong	Pflug Archiv (3.6)	2009	205	The authors of this study showed that TPCN2 exhibits the fundamental characteristics of native NAADP-dependent Ca^{2+}-release channels. After being activated by low-nanomolar concentrations of this second messenger, TPCN2 causes the release of intracellular Ca^{2+}, but it is desensitized by micromolar concentrations.

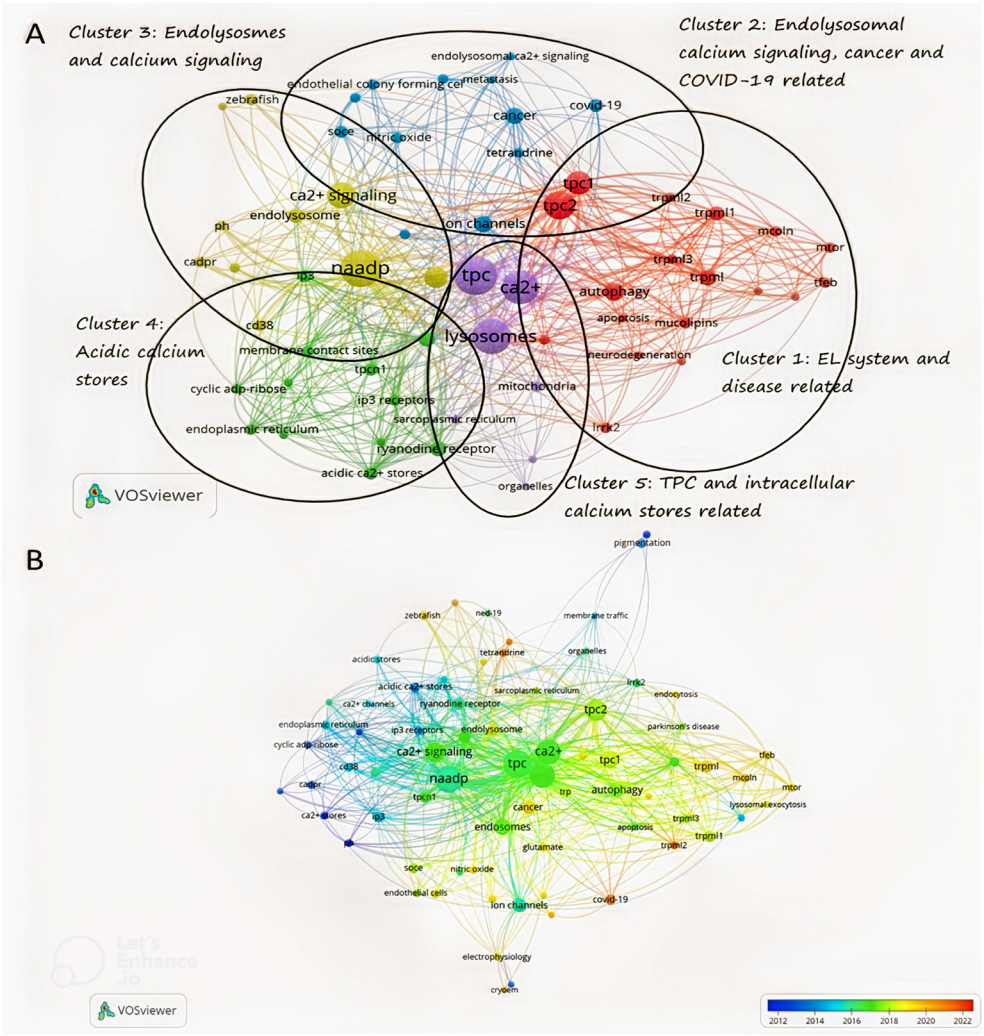

Figure 3: Visualisation maps of author keywords found in literatures on TPC. (A) Network of author keywords of TPC research, (B) Map of emerging keywords in TPC publication (blue: earlier publication year; red: later publication year).

cluster are linked to EL-related diseases. Keywords in the purple cluster are associated with intracellular calcium stores while keywords in the green cluster are related to intracellular calcium signalling. The yellow cluster contains keywords that are linked to EL calcium signalling. An example is NAADP which is one of the endogenous ligands of TPC. Meanwhile, the keywords in the blue cluster are connected to cancer. One example is metastasis, a process via which malignant cells disseminate to distant anatomical sites within the body.

To demonstrate the evolution of keywords in TPC research, the emerging keywords map was constructed using VOSviewer (Fig. 3B). Emerging keywords are topics that have recently garnered attention but have not yet been extensively investigated. Thus, emerging keywords represent chances for future studies. The keywords were colour-coded to categorise them according to their respective publication years. The colour blue indicated earlier publication year, while the colour red denoted a more recent one. COVID-19, TRMPL2, and tetrandrine were the emerging keywords in TPC research, recently trending between 2021 to 2022.

DISCUSSION

The current bibliometric analysis focuses on TPC and includes a thorough review of 292 papers pertaining to this subject matter. Following the release of the first article in 2000 on the cloning of TPC, research output on TPC was low and remained relatively flat until the inaugural paper on TPC as NAADP-mediated calcium channel was released in 2009. Since then, research on TPC has progressively increased with slight fluctuations over the years. The highest peak was observed in 2021 with 35 publications. Interestingly, it is anticipated that this record will be surpassed based on the number of publications as of 2nd August 2022 which was standing at 30 articles. This trend indicated that TPC continues to receive attention from researchers. This could be due to reports on its roles in various physiological and pathological events. The emergence of more selective pharmacological modulators of TPC could also facilitate research on this channel. Nowadays, TPC2 is a hot topic following reports on its potential as a therapeutic target for COVID-19 and it is anticipated that research on TPC will continue to expand in the next years.

Out of 43 countries involved in TPC research, the UK was the most productive country, followed by the USA. Indeed, both countries collaborated in the first publication describing TPC as a novel NAADP-mediated calcium channel in 2009, which was published in Nature. The UK was actively involved in the research on NAADP, the calcium mobilising second messenger which has led to the discovery of TPC. While the US is leading in the research on calcium channels (13) and TRP channels (14).

A total of 160 authors participated in publications related to TPC research. Antony Galione, Sandip Patel, John Parrington and Christian Grimm were involved in more than 20 publications on TPC. Moreover, Galione and Patel were both highly cited, receiving more than 700 co-citations. The most productive authors have focused on the role of TPC in Ca^{2+} signalling, lysosomal trafficking, muscle contraction, autophagy, neoangiogenesis, and insulin secretion (5). Parrington has also worked on the role of TPC in cancer and adipose tissue while Galione has worked on the role of TPC in the development of neurons, myogenesis, and plant cells. Patel has mostly conducted research on the role of TPC in ebolavirus entry, and cell pigmentation. Ruas has investigated the importance of TPC in ebolavirus entry, TPC structure, and the role of TPC/ Ca^{2+} signalling in heart cells. These prolific authors also collaborated and published works jointly. For instance, there was an active collaboration between Parrington, Galione, and Ruas. Similarly, there was an active collaboration between Biel, Grimm, Chao, and Ngyuen. Another diligent network existed between Patel, Brailouie, and Jaha.

The article authored by Xiuyuan Ou in 2020 entitled "Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV" was cited the most with total citations of 1668, followed by the paper by Calcraft in 2009 entitled "NAADP mobilises calcium from acidic organelles through two-pore channels", with 563 total citations, and the paper by Xu in 2015 entitled "Lysosomal physiology" with total citations of 542. In general, the top 10 highly cited papers focused on the physiological role of TPC, its role in the release of calcium and other ions from the acidic store, and the role of TPC in diseases including cancer, COVID-19, pigmentation, and autophagy. Below, we delve further into selected research hotspots and emerging keywords of TPC publications.

TPC and Autophagy

Autophagy, a crucial cellular catabolism and recycling process transports unwanted intracellular components, such as damaged organelles and foreign substances, to lysosomes for degradation (15). An intriguing attribute of autophagy is its bipolar character in cancer which is supported by plenty of studies (16, 17). It suppresses tumour growth during the benign and tumour initiation stages, but as the cancer progresses, it shifts its mode from suppressing to promoting the tumour growth. Cancer cells rely on autophagy to expand when their metabolic and biosynthetic needs increase concurrently (15). As a result, autophagy is connected to cancer-related characteristics such as metastasis, tissue invasion, and epithelial-mesenchymal transition (18). Several research have also shown a correlation between autophagy and the reprogramming of tumour metabolism and therapeutic resistance (19).

Both basal and induced autophagy are regulated by Ca^{2+} signalling (20). TPC and other calcium-permeable channels are involved in controlling autophagy in a variety of cell types. A positive or negative regulation of autophagy by TPC has been demonstrated (21). Cell type, protein expression, and cell state are suggested to have an impact on TPC's function (22). The increase of LC3-II and syntaxin 17 (STX17)-positive autophagosomes was caused by overexpression of TPC which impeded the fusion of autophagosome and lysosome. While TPC-deficient cells displayed a low number of autophagosomes.

TPC and COVID-19

Previous studies have shown that inhibition of TPC through pharmacological means can impede viral infections caused by pathogens such as the Middle East respiratory syndrome coronavirus (MERS-CoV) (23) and the Ebola virus (24). These viruses enter the cells of their host organisms through endocytosis, and they may exit the EL system through endosomes. EL trafficking is facilitated by TPC and blocking it disrupts this process. Like forementioned viruses, studies have demonstrated that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could also be prevented using pharmacological inhibitors of TPC (25,7). According to the findings, TPC inhibitor tetrandrine significantly decreased the entry of SARS-CoV2 pseudovirions into HEK 293 cells that expressed the human angiotensin-converting enzyme 2 (ACE2), the main route for SARS-CoVs invasion (25). Another study revealed that naringenin, a TPC2 inhibitor, has a significant antiviral impact in vitro against the human coronaviruses HCoVOC43, HCoV229E, and SARS-CoV-2 (7). Given its involvement in the modulation of immunological responses and the reduction of ACE2 expression in rat kidneys, naringenin could be a useful therapeutic agent in COVID-19. Naringenin can diminish airway inflammation and lung damage in vivo by reducing neutrophil infiltration.

The findings of utilising pharmacological inhibitors to study TPC2's role in preventing viral infection were supported by genetic silencing of TPC2. The infection of Huh7.5 cells with the coronavirus HCoV 229E resulted in a notable decrease in infection upon TPC2 silencing, indicating the active involvement of TPC2 in the mechanisms underlying coronavirus infection (7).

Studies on TPC in the context of cardiovascular disease and COVID-19 are also expanding. COVID-19 patients with pre-existing cardiovascular disease are at risk of more severe complications such as thromboembolic events and myocardial injury (26). Given the substantial involvement of TPC2 in the cardiovascular system, including the regulation of nitric oxide release and blood pressure (27), as well as secretion of von Willebrand factor and platelet aggregation (28), there is a proposition to consider TPC2 as a viable target for treating cardiovascular disorders in COVID-19 patients (29). The postulation that inhibition of TPC2 could mitigate the harmful effects of COVID-19 on the cardiovascular system must be firmly established.

TPC and Cancer

TPC is expressed in various cancerous cells, including breast (30), bladder cancer, and liver cancer cells (31). The NAADP/TPC/Ca^{2+} signalling pathway is involved in a variety of cancer-related processes from metastasis to carcinogenesis (32) and the role of TPC in cancer hallmarks has been reviewed recently (33).

Nguyen et al. (31) has demonstrated the importance of TPC in the EL Ca^{2+} release and proliferation of metastatic colorectal cancer cells. The authors have also shown the roles of TPC in the adhesion and migration of T24 human urinary bladder cancer cells and Huh7 human liver cancer cells via pharmacological inhibition with Ned-19 and tetrandrine. Additional research in a mouse model implanted with 4T1-Luc cells showed that TPC2 silencing, tetrandrine treatment, and Ned-19 treatment all inhibited the establishment of lung metastases.

Studies have shown that TPC plays a part in drug resistance. In a drug-resistant leukaemic cell line, TPC2 mRNA expression was shown to be elevated (34). Vincristine-resistant CEM cells (VCR-R CEM) had 2-fold TPC2, which promotes cell growth. These cells proliferated or grew more slowly than the wild type when TPC2 was knocked out. Additionally, leukaemic cell line TPC2-deficient cells had increased vincristine sensitivity.

TPC Inhibitors

Due to the importance of TPC in a wide range of pathophysiological processes such as metabolism, cell growth and development, cancer progression, and COVID-19, discovering specific pharmacological modulators will be crucial for both scientific study and drug discovery (7). The majority of TPC inhibitors are pore-blockers. Traditional voltage-gated Ca^{2+}-channel blockers interact with TPC at high concentrations. Verapamil, for example, blocks TPC1 (35) and TPC2 (36) currents as well as NAADP-induced Ca^{2+} release (37). Tetrandrine, a broad-spectrum channel blocker, is used to inhibit TPC2 and TPC1, and structural modification of this drug has revealed more effective analogues for TPC2, albeit these analogues may not always distinguish TPC2 from TPC1 or TRPMLs (38). Another blocker, naringenin, has been displayed to specifically inhibit mobilisation of EL Ca^{2+} by TPC2 in response to agonists, namely VEGF and histamine (39).

CONCLUSION

This study represents the inaugural bibliometric analysis that showcases the worldwide patterns and prospective advancements in the field of TPC research. Our findings suggest that research on TPC will continue to be a significant and developing area of academic study. The importance of TPC in a wide range of pathophysiological processes has sparked interests in researchers leading to increased research output on TPC. The emergence of highly selective pharmacological modulators of TPC has also facilitate the development of research on this channel. Based on the emerging keywords map, we can conclude that autophagy, cancer, COVID-19 and TPC inhibitors were examples of areas that could be further explored in the coming years. It is hoped that the outcomes of our research could serve as a valuable point of reference for scholars who are inclined towards undertaking further investigations within this specific topic. Persistent effort in gaining a comprehensive understanding of the pathophysiological functions of TPC may firmly establish its therapeutic potential in diverse human disorders.

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