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2012-2022 TRPC6 channel and podocyte research trends: A bibliometric study

Junhua Deng[1], Zengbo Huang[1], Sanju Yang[1], Yunguang Liu[1*]

[1]Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
[*]Corresponding author: Lyg9226@163.com

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Abstract: TRPC6, fully known as transient receptor point cation channel 6, has attracted increasing attention as a member of the TRPC family[1] The results of many studies prove that it is involved in several physiological functions in the kidney [2,3], in particular, it is expressed as an important ion channel in kidney podocytes and is important for the regulation of calcium homeostasis in podocyte[4,5]. In this review, we hope to analyze the research hotspots and future research directions in the field of TRPC6 and podocytes by using some bibliometric analysis software.

1. Introduction

The TRP superfamily has six subfamilies (TRPC, TRPM, TRPML, TRPV, TRPP, and TRPA1), and the TRPV1 channel studied by the 2021 Nobel Laureate is a small branch of the TRPV subfamily [6].The TRPC6 non-selective cation channel we need to study is a member of the TRPC subfamily, which includes TRPC1-7 and is involved in various physiological and biochemical actions of organisms by forming cation channels in the plasma membrane[1] .A well-known researcher in the field of TRPC6 is Winn [7],he was the first to clone the TRPC6 gene, which encodes the TRPC6 channel protein, from patients with familial FSGS in 2005. He is a landmark figure in TRPC6 channel research. Under cryo-electron microscopy, the TRPC6 protein structure is composed of amino acids folded into two long helices, CH1 and CH2. CH1 runs from the periphery to the center of the channel and is attached to CH2 by a 90 ° turn. The TRPC6 protein is a 6-times transmembrane protein composed of 931 amino acids. The small pore region between its 5th and 6th transmembrane proteins forms the cation channel[8.9]

The podocytes are cross-linked with each other to form a finger-like cross-linked fence-like structure called the lacunar pore, which is covered with a 4-6 nm film called the lacunar membrane SD.Recent studies have shown that podocytes are one of the important cells that make up the glomerular basement membrane[10] ,and abnormalities in the morphology, number and function of podocytes caused by various injury factors can cause proteinuria and eventually lead to renal function impairment[11-13] .Podocytes likewise play an important role in renal diabetic neuropathy, and many studies have demonstrated that podocyte loss and death are the earliest glomerular manifestations of renal diabetes[14-16].

The connection between his two is that podocyte-associated proteins are currently more intensively studied, such as podocin (encoded by NPHS2), nephrin (encoded by NPHS1), WT1 (encoded by

WT1), TRPC6 (encoded by TRPC6), and α-actinin (encoded by ACTN4) [17].The study of TRPC6 gene mutations leading to podocyte damage has been a research trend in recent years[18-20].

Bibliometrics is a way of summarizing and summarizing information about the title, year, institution, country, keywords, abstracts, etc. It represents not only a categorization and organization of the literature by the organizer, but also a summary and understanding of the field of study, a dissection of the cooperative relationship between authors, institutions or countries, and an anticipation of future developments in the field [21].Today, several fields of medical research are already applying bibliometrics as a research method, for example neurology[22], psychiatry[23], immunology [24],pediatrics [25],and oncology[26].

To the best of our knowledge, no bibliometric article was searched so far regarding TRPC6 channel with podocyte. To complement this field, scientific publications related to TRPC6 channnel and podocyte were searched in a time frame (2012-2022) using bibliometric research tools and summarized. The aim is to help researchers to recognize and understand this field.

Data source and search strategy:

The WOS database is a well-established citation database that also has great influence and authority worldwide. Its Web of Science core database includes more than 20,000 of the world's most authoritative and high-impact academic journals. We chose the WOS database as our source of statistics. All publications related to TRPC6 channnel and podocyte were obtained from the Web of Science Core Collection. The search was conducted as follows: TS=(TRPC6 and podocyte or transient receptor channnel 6 ANDpodocyte). The publication dates are limited to 2012-01-01 to 2022-12-30. Only journal and review articles were retained, and all non-English articles were excluded. Two authors conducted an independent search and screening of publications. In case of doubt, the third reviewer resolved differences through discussion or arbitration if necessary **(Figure 1).**

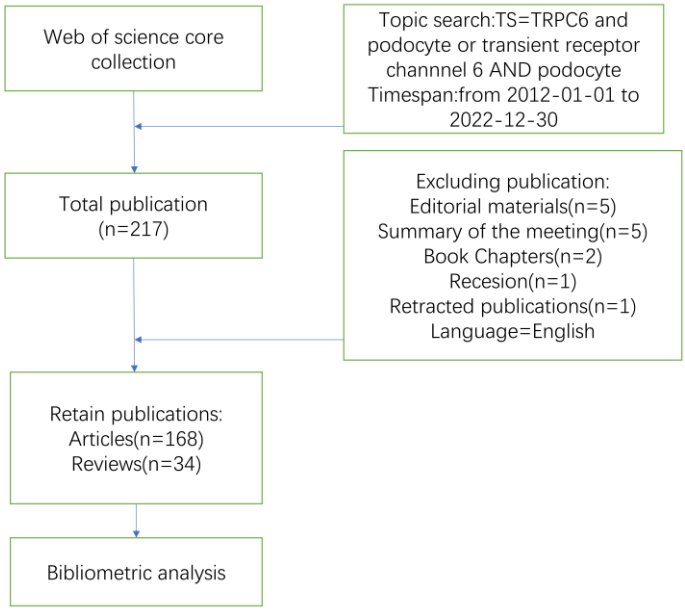

Figure 1: Search Flow Chart.

2. Data Collection

Relevant data is retrieved from the WOS database and downloaded in full record format. Then imported into VOSviewer (version1.6.19), Microsoft Excel (version 2022) and Citespace (version6.2.R2). The data imported into citespace are saved in the format "download_202". Because

the WOS database is updated with articles, we have to search and download our data on the same day. (April 26, 2023).

3. Statistical Analysis

We use Excel to create tables to analyze the number of publications, citation rates, and centrality. Excel is also used to create graphs of the number of publications published annually and the percentage of journals and reviews of publications. Bibliometric was used to count and graph the most cited literature. Bibliometric is used to count the most cited documents and to create statistical graphs. VOSviewer is used to build country/region density maps and a network of links to authors and institutions. CiteSpace is used to study the connection and strength of different nodes, calculate centrality, and perform cluster analysis and bursting of keywords. The citespace parameter is set to the time from 2012-01-01 to 2022-12-30, with a time slice of one year. The node type is adjusted as desired (select country, institution, keyword, etc.).g-index(k=25). Using path pruning will make these images more aesthetically pleasing.

4. Overall Distribution

As of December 31, 2022, the total citation count of these articles in the bibliometrix citation report was 6713, with an average citation count of 22.19 per paper. If the research becomes a current hot topic or trend, more researchers and papers will be published in the whole field, and the number of citations will naturally be higher. An increase in the volume of literature in a field usually indicates that there are scholars who are continuing to focus on and work deeply in the field (Figure 2A).WoSCC included 202 publications between 2012 and 2022, including 168 journals and 34 reviews **(Figure2B)**. It can be seen that the number of publications has been on an upward trend during this decade.

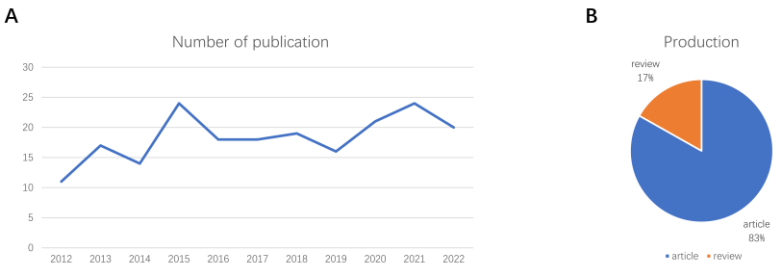

Figure 2: (A) Line graph of the number of publications per year on the TRPC6 channel and podocyte fields. (B) Pie charts of journals and reviews.

4.1 Country/Region Analysis

A total of 99 countries/regions published articles on TRPC6 and podocyte. The strongest density

was found in the USA, proving the importance of the USA in the field of TRPC6 and podocytes(Fig.3 A).As shown in **(Fig.3 B)**, The country/region network collaboration diagram drawn with Citespace has 34 nodes and 45 links. The larger dots represent more publications, and it can be seen that the dots in the US and China are larger, proving that these two countries have more publications than the other countries on the diagram. As we can see from the table**(Table 1)**, the first in the number of publications is the United States with the number of publications (n=78), the second in the number of publications is China with the number of publications (n=75) and the third in the number of publications is Germany with the number of publications (n=22).The top node centrality ranking is the United States (centrality = 0.74), which shows that the United States has the most influence in this field and has more cooperation and exchange with other countries or regions**(Table 1)**. The three countries with the highest number of citations were first the United States (n = 2430), second China (n = 1241) and third Germany (n = 605) **(Table 1)**.

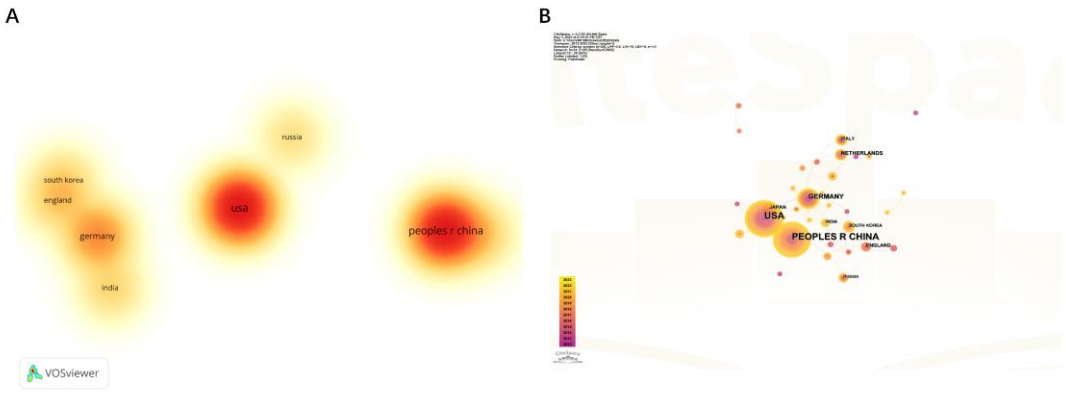

Figure 3: (A) VOSviewer density of distribution of countries/regions in publications;(B) CiteSpace network map of countries/regions in the publication.

Table 1: Top 10 countries or regions in terms of number of publications in the TRPC6 channel and podocyte.

Rank	country	TP	PERCENTAGE	TC	centrality
1	usa	78	38.61%	2430	0.74
2	peoples r china	75	37.13%	1241	0
3	germany	22	10.89%	605	0.25
4	netherlands	12	5.94%	347	0.08
5	japan	9	4.46%	133	0
6	england	8	3.96%	262	0.11
7	india	7	3.47%	53	0.42
8	italy	6	2.97%	91	0.03
9	south korea	6	2.97%	192	0.01
10	russia	5	2.48%	218	0

4.2 Institutional Analysis

A total of 616 institutions have published articles in areas related to TRPC6 channel and podocytes. Network plots from both Vosviewer software **(Figure4 A)** and Citespace software **(Figure4 B)** demonstrate that the University of Houston is a major contributing institution in the field of TRPC6 and podocyte research. The network graph of these institutions shows 213 nodes and 510 links **(Fig4 B).** Node centrality indicates that the highest node centrality is at Cologne University (centrality = 0.13), the second highest node centrality is at the University of Houston (centrality = 0.10), and the third highest node centrality is at Harvard University (centrality = 0.04), demonstrating that these three institutions play a greater role in TRPC6 channel and podocyte research than other institutions. These findings suggest that US institutions dominate the field of TRPC6 channel research. The top three institutions in terms of number of publications were the University of Houston (n = 21), Baylor University (n = 13), and Radboud University (n = 12). The three most cited institutions for publications were first the University of Houston (n = 722), second Baylor University (n = 539), and third the University of Cologne (n = 415) **(Table 2)**.

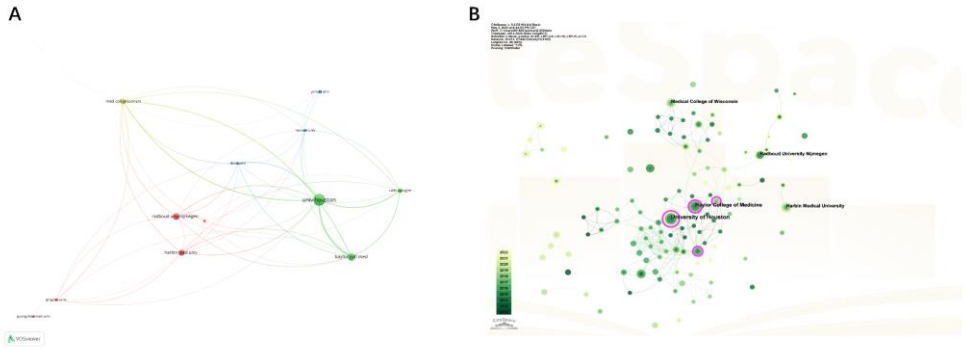

Figure 4: (A) A network diagram of major institutions with a high number of publications produced with vosviewer. The purple circle represents greater centrality.

Table 2: Top 10 institutions with a high number of publications in the field of TRPC6channel and podocytes.

Rank	Institution	**TP**	**Percentage (%)**	TC	Centrality
1	univ houston	21	10.40%	722	0.1
2	baylor coll med	13	6.44%	539	0.01
3	radboud univ nijmegen	12	5.94%	347	0
4	harbin med univ	11	5.45%	245	0
5	med coll wisconsin	10	4.95%	415	0
6	univ cologne	8	3.96%	258	0.13
7	duke univ	5	2.48%	155	0.01
8	harvard univ	5	2.48%	135	0.04
9	qingdao univ	5	2.48%	30	0.01
10	nanjing univ	5	2.48%	112	0

4.3 Analysis of Cited Journals

The 202 articles were from 108 different journals. **Table 3** shows that the number of citations J AM SOC NEPHROL (2012) ranked first with 195 citations, followed by KIDNEY INT (2012) with 172 citations and AM J PHYSIOL-RENAL (2012) with 163 citations. From Figure 5, we can see that the dots corresponding to these three journals are the largest.It can be seen that these three journals are important journals in the field of TRPC6 channel and podocyte, and researchers will mainly obtain knowledge about this field from these three journals.

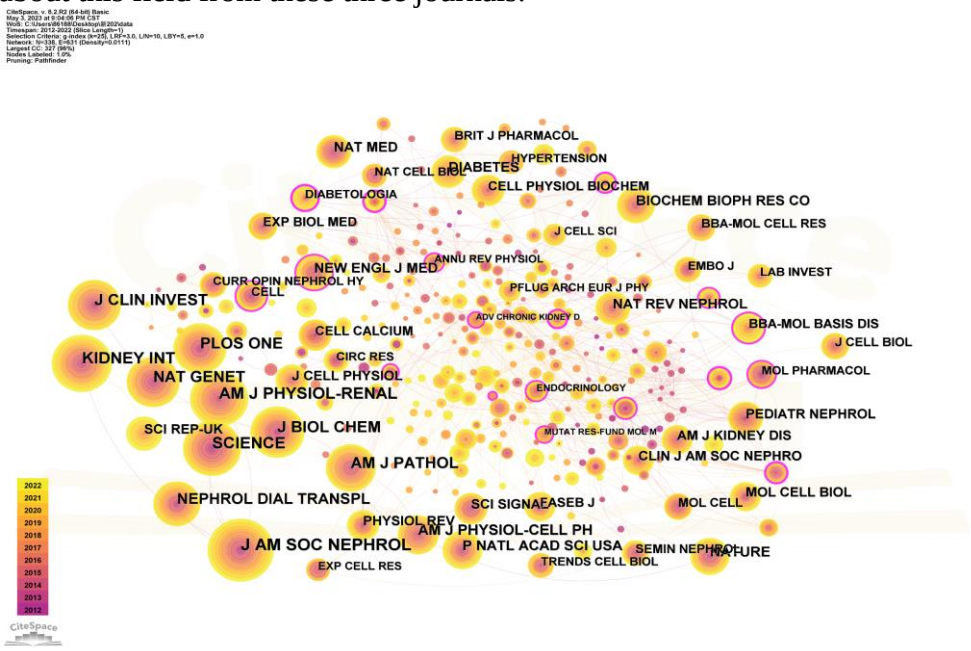

Figure 5: Network diagram of the major journals with the highest number of citations.

Table 3: Top 10 most cited institutions in the TRPC6 channel and podocyte fields.

Rank	Jounal	TC
1	J AM SOC NEPHROL	195
2	KIDNEY INT	172
3	AM J PHYSIOL-RENAL	163
4	SCIENCE	149
5	J CLIN INVEST	141
6	NAT GENET	138
7	J BIOL CHEM	136
8	AM J PATHOL	126
9	PLOS ONE	126
10	NEPHROL DIAL TRANSPL	110

4.4 Author Analysis

A total of 1093 authors have published articles in the field of TRPC6 channel and podocyte. Notably, Dryer, stuart e published the articles with the highest number of publications in this statistic (n=17). Second place isKim, eun young (n=13). The third place isStaruschenko, alexander (n=10). The most cited published articles are: Dryer, Stuart E (n=620), kim, eun young (n=424), staruschenko, alexander (n=415). **(Table 4)** .The authors' network diagram shows that it consists of 272 nodes and

434 links **(Figure 6B)**. Figure 6C author's yield timeline diagram indicates Dryer, Stuart E basically works every year and he has contributed a lot to this field.

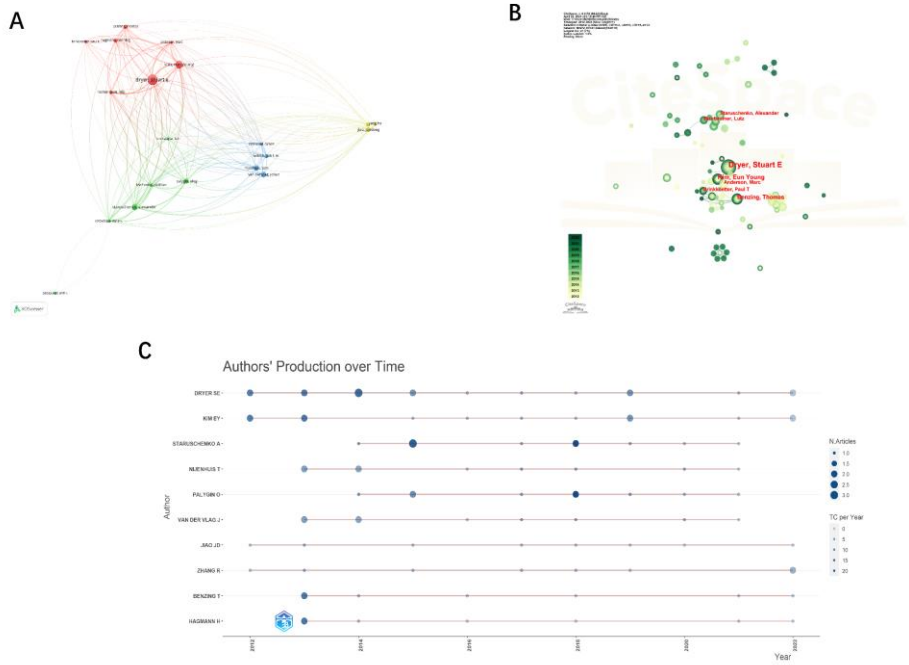

Figure 6: (A) Network diagram of the main authors in this field by Vosviewer (B) Network diagram of the main authors in this field by CiteSpace. (C) Timeline diagram about the authors by Bibliometric.

Table 4: Top 10 authors in number of publications in TRPC6 channel and podocyte field.

Rank	author	TP	Percentage(%)	TC
1	dryer, stuart e	17	8.42%	620
2	kim, eun young	13	6.44%	424
3	staruschenko, alexander	10	4.95%	415
4	palygin, oleg	8	3.96%	280
5	benzing, thomas	7	3.47%	195
6	hagmann, henning	7	3.47%	195
7	roshanravan, hila	6	2.97%	217
8	levchenko, vladislav	6	2.97%	248
9	anderson, marc	5	2.48%	342
10	ilatovskaya, daria v	5	2.48%	269

4.5 Most Cited Literature

The most cited literature worldwide and their authors. The top three authors are ZHOU LL,, with 151 citations and an average of 16.78 citations per year[27],second is XU S, with 117 citations and an average of 13 citations per year [28],and third is KIM EY, with 102 citations and an average of 8.7 citations per year[29].These three authors have made great co-presentations in this field. **(Figure 7, Table 5)**

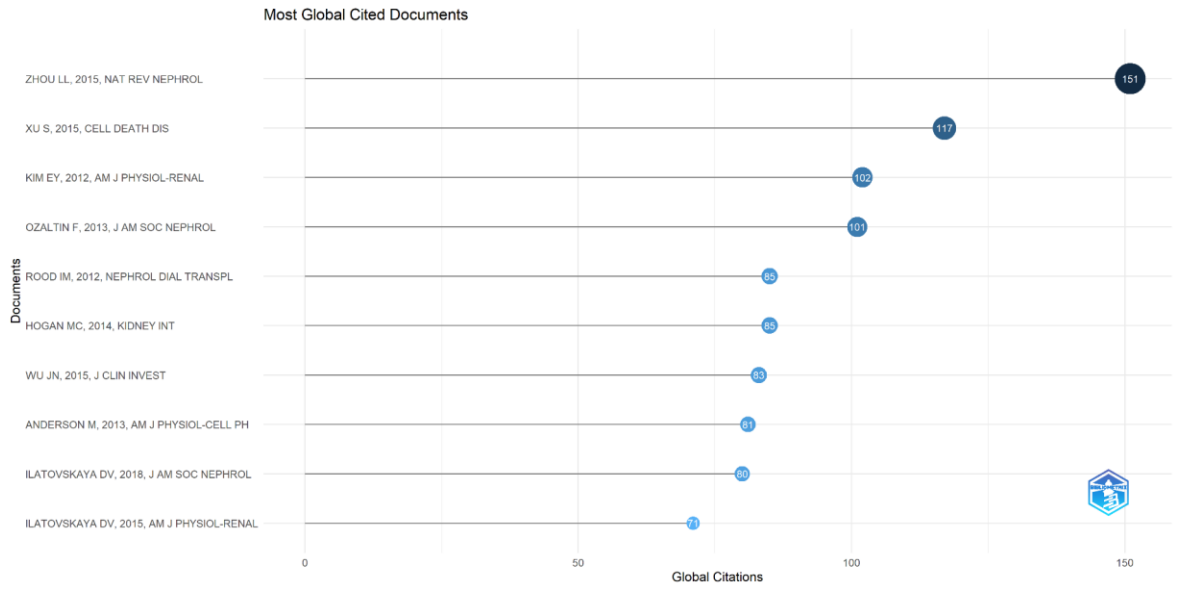

Figure 7: Top 10 documents in number of publications in TRPC6 channel and podocyte field by Bibliometric.

Table 5: Top 10 documents in number of publications in TRPC6 channel and podocyte field.

Paper	DOI	Total Citations	TC per Year	Normalized TC
ZHOU LL, 2015, NAT REV NEPHROL	10.1038/nrneph.2015.88	151	16.78	4.04
XU S, 2015, CELL DEATH DIS	10.1038/cddis.2015.331	117	13	3.13
KIM EY, 2012, AM J PHYSIOL-RENAL	10.1152/ajprenal.00423.2011	102	8.5	2.68
OZALTIN F, 2013, J AM SOC NEPHROL	10.1681/ASN.2012090903	101	9.18	2.57
ROOD IM, 2012, NEPHROL DIAL TRANSPL	10.1093/ndt/gfr771	85	7.08	2.23
HOGAN MC, 2014, KIDNEY INT	10.1038/ki.2013.422	85	8.5	2.12
WU JN, 2015, J CLIN INVEST	10.1172/JCI81061	83	9.22	2.22
ANDERSON M, 2013, AM J PHYSIOL-CELL PH	10.1152/ajpcell.00095.2013	81	7.36	2.06
ILATOVSKAYA DV, 2018, J AM SOC NEPHROL	10.1681/ASN.2018030280	80	13.33	3.88
ILATOVSKAYA DV, 2015, AM J PHYSIOL-RENAL	10.1152/ajprenal.00186.2015	71	7.89	1.9

4.6 Analysis of Cited Authors

The most cited author is REISER J (2012) with a citation count of 130, second is WINN MP (2012) with 126 citations and third is Moeller CC (2012) with 74 citations **(Table 6)**. This shows that these three scholars are the leading scholars in this field. Node centrality is 0.29 for ANDERSON M, 0.27 for FAUL C, and 0.14 for Moeller CC **(Table 6)**. The strongest node centrality is ANDERSON M. It can be seen that ANDERSON M plays an indispensable role in this field **(Figure 8)**.

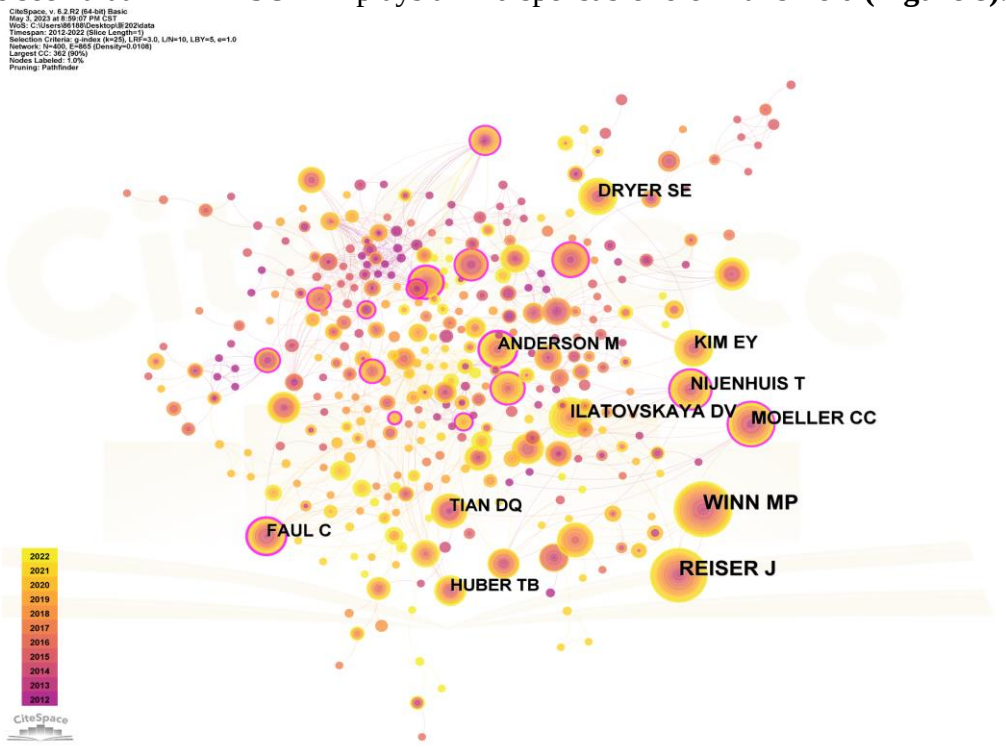

Figure 8: Network map of the main cited authors in number of publications by CiteSpace.

Table 6: Top 10 cited authors in number of publications in TRPC6 channel and podocyte field.

Rank	author	TC	centrality
1	REISER J	130	0.05
2	WINN MP	126	0.1
3	Moeller CC	74	0.14
4	ILATOVSKAYA DV	72	0.04
5	NIJENHUIS T	66	0.12
6	KIM EY	65	0.03
7	DRYER SE	61	0.07
8	FAUL C	58	0.27
9	TIAN DQ	52	0.08
10	ANDERSON M	51	0.29

4.7 Keyword Analysis

The 202 articles collected in this article include 953 keywords. The top six keywords for node centrality are ativation (centrality = 0.15), fsgs (centrality = 0.16), expression (centrality = 0.13),

sugar kidney (centrality = 0.11), trpc (centrality = 0.12), and foot cell damage (centrality = 0.12) **(Table 7)**. The keyword network graph contains 276 nodes and 2590 links. **(Figure 9A)**. In conclusion, the role of trpc6 channel activation is of primary interest to researchers.

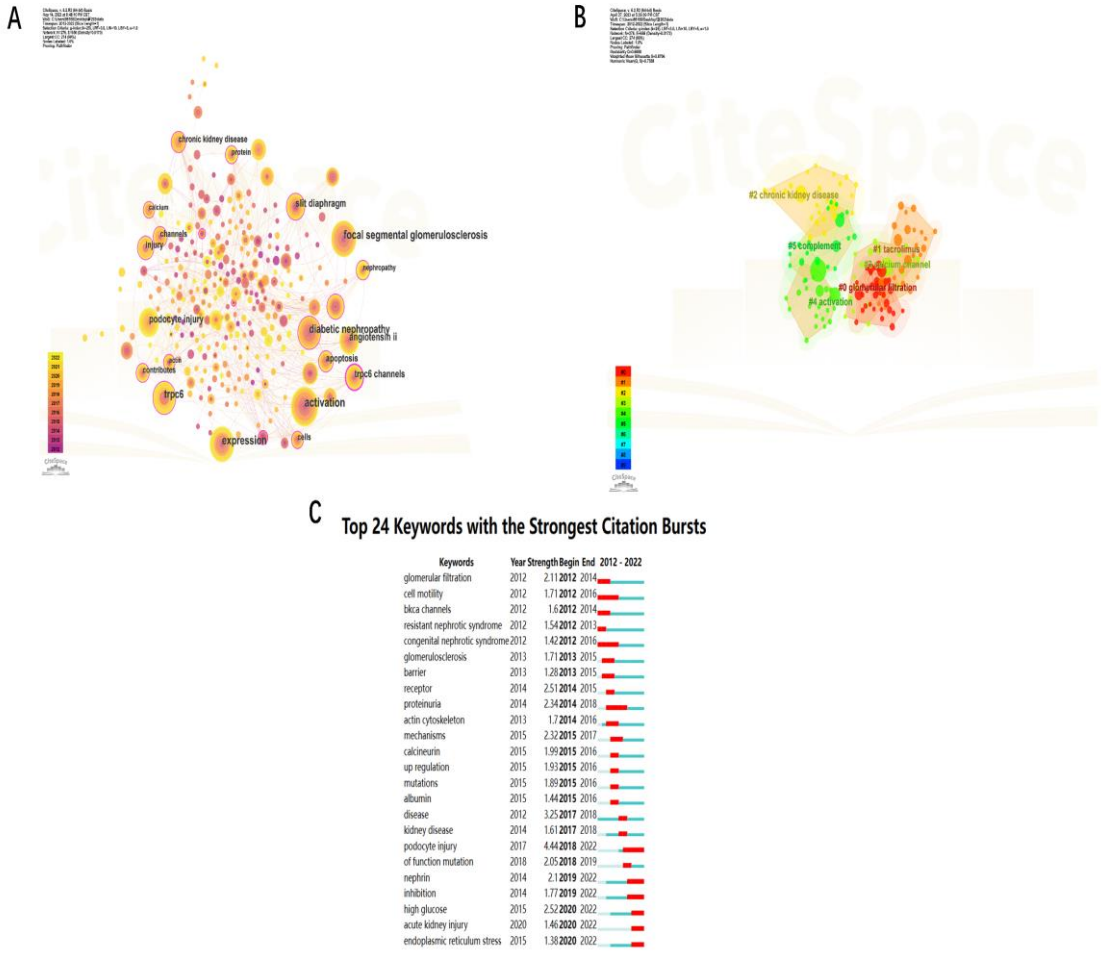

Figure 9: (A) Network map of the main key words in number of publications by CiteSpace. (B) Keyword clustering chart top 6 by Citespace. (C) The first twenty-four keyword outbreak chart by Citespace.

Table 7: Top 6 key words in number of publications in TRPC6 channel and podocyte field.

Rank	key word	TC	centrality
1	activation	63	0.15
2	fsgs	57	0.16
3	expression	54	0.13
4	diabetic nephropathy	41	0.11
5	trpc6	40	0.12
6	podocyte injury	32	0.12

Keyword clustering analysis showed that 953 keywords were classified into 6 major clusters (Q value = 0.67, S value = 0.87): #0glomerular filtration, #1tacrolimus, #2chronic kidney disease, #3calcium channel, #4activation , and #5complement **(Figure 9B)**. Glomerular filtration rate and the efficacy of tacrolimus are the focus of trpc6 vs. podocytes. Glomerular filtration rate is the main method of testing renal function usually used in clinical practice to develop treatment plans. In addition, tacrolimus is an important drug for immunization of renal podocyte injury. trpc6 mutations

often lead to chronic kidney disease. trpc6 is a non-selective calcium channel. Therefore, these are the main issues in the field of trpc6 and podocyte research.

The red bars in the image indicate the time period of the citation spike. Changes in the intensity and duration of outbreaks indicate the changing content and hotspots of research in the TRPC6 channel and podocyte field. We can see from the change in timing of the sudden keywords shows that for burst detection, podocyte injury (intensity = 4.44, 2018-2022), disease (intensity = 3.25, 2017-2018) and high glucose (intensity = 2.52, 2020-2022) showed strong bursts **(Figure 9C)**, reflecting the latest research trends in this field.

5. Discussion

Based on the published results, keywords co-occurrence, we listed the hot spots and areas of TRPC6 research from TRPC6 activation, TRPC6 and familial fsgs, TRPC6 expression, TRPC6 and glycogen kidney, and podocyte injury.

5.1 TRPC6 and activation

As a non-selective calcium channel, TRPC6 ion channel activation in podocytes leads to elevated continuous calcium inward flow and promotes apoptosis in glomerular thylakoid cells[30] .Scholars using cncp to activate TRPC6 channels caused apoptosis in renal HK-2 cells [31],found that activation of TRPC6 channels by using angiotensin II caused extensive fusion of podocytes[32].

5.2 TRPC6 and FSGS

TRPC6 has been closely associated with FSGS since it was first cloned from patients with familial focal stage glomerulosclerotic disease. According to the report， a familial case showed that a woman 35 years old with nephrotic syndrome, mother with CKD and brother with proteinuria, her and her mother's kidney puncture biopsies indicated a TRPC6 gene mutation, D873fxx878 [33].The researchers knocked down the actin-binding protein TRPC6 gene as a way to reduce the expression of TRPC6 protein for the purpose of protecting podocytes [34].Kim EY et al,found that deletion of 239 bp within TRPC6 exon 2 resulted in decreased urinary protein excretion and reduced interstitial changes and renal fibrosis in rats with TRPC6 deletions compared to rats from the same litter as wild-type TRPC6[35].Study shows suPAR induces oxidative stress in podocytes and driver signaling upregulates TRPC6 via src family of kinases leading to podocyte loss[36].It was found that TRPC6 inactivation was effective in protecting the glomerulus, but only to the extent of protecting the glomerular lumen[37].

5.3 TRPC6 Expression

TRPC6 overexpression significantly reduces podocyte processes and DEX can rescue these changes by blocking the TRPC6 channel, DEX maintains the structural and functional integrity of SD by blocking the TRPC6 signaling pathway, which is important in the anti-proteinuric process [38].Podocyte desynaptation leads to reduced signaling communication with synaptic proteins and the cytoskeleton, which results in overexpression of TRPC6 protein, causing excessive calcium inward flow and affecting the normal physiological function of podocytes[34].It was found that metformin protects podocytes by reducing the surface expression of TRPC6 through the AMPK pathway in the renal hyperglycemic state, thus serving to reduce the permeability of the filtration membrane[39].

5.4 TRPC6 and the Diabetic Nephropathy

Glucose causes diabetic nephropathy by activating the renin-angiotensin system, leading to glomerular foot cell damage[40].Another similarly argues that the angiotensin II/TRPC6/NFAT axis is the treatment for diabetic nephropathy[41].KL inhibits TRPC6 expression, attenuates glycogenic kidney podocyte injury, and reduces proteinuria[42].

5.5 Podocyte Injury

Increased TRPC6 expression in 1,25-D3-deficient 25-hydroxy-1-alpha-hydroxylase-activated knockout mice is accompanied by podocyte podocyte loss and proteinuria[43] .TRPC6 induces glomerular podocyte injury and proteinuria, and clinical use of sildenafil to inhibit TRPC6 promoter activity ameliorates podocyte injury and prevents proteinuria[44].Data show that glomerular NOS-NO-SGC-CGMP-TRPC6 channels prevent podocyte injury, NO and RIOCIGUA stimulate podocyte CGMP synthesis,reduction of adriamycin-induced TRPC6 expression to protect podocytes[45] .

6. Conclusion

This study provides a statistical description of the number of publications and citations by country, institution, and author, as well as insight into the most cited articles, journals, and authors. Cooccurrence, clustering and emergent words were detected for keywords in the domain. Through these methods, we have a general study of the field and a clear understanding of the hot spots in the field. This serves as an inspiration for the future direction of our research. In these years, most researchers have studied TRRPC6 activation, TRPC6 and FSGS, TRPC6 expression, TRPC6 and diabetic nephropathy, and podocyte injury. Keyword clustering refines the topic distribution, which can be summarized as glomerular filtration, tacrolimus, chronic kidney disease, calcium channel, activation, and completion. The specific functional mechanisms of TRPC6 channelh and podocyte are still unclear, and many questions remain to be solved in the field of TRPC6 channel and podocyte.

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