

The past and future of Piezo

A scientometric review

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Abstract

Background: As we all know, this Nobel Prize is awarded to uncover the mechanism of “a glass of cold milk providing instant relief when eating a spicy hot pot”; the key factor, Piezo, has therefore become a clinical research hotspot. Most importantly, the factor of Piezo has been increasingly considered when analyzing the majority of common clinical diseases. The Piezo has entered a new stage and has made a series of progress. This study mainly outlines the knowledge map and detects the potential research hotspots by using bibliometric analysis.

Methods: The core collection database of WoS was used to retrieve the bibliographic records related to Piezos from January 1, 2010 to October 8, 2021. CiteSpace was utilized to generate and analyze visual representations of the complex data input.

Results: Overall, the number of Piezos publications has shown a significant upward trend since 2010. There were 902 research publications referenced a total of 19,095 times. The United States and China are the two nations with the highest number of published articles in this discipline. The institutions with the most publications are Scripps Research Institute and the University at Buffalo (SUNY-Buffalo). The primary topics of investigation are “endothelial cell” “xerocytosis” “current” “calcium”, “mutation” “activated ion channel” “Ca²⁺ influx” “protein” “smooth muscle” and “nociception”. Ardem Patapoutian and Frederick Sachs are the two most prolific authors of scholarly articles. The gene expression is the current focus of research in this topic.

Conclusions: Piezo is rapidly developing. This knowledge will be utilized extensively in the process of developing treatments for many diseases. Current research focuses mostly on gene expression.

Abbreviations: WoS = Web of Science.

Keywords: bibliometric analysis, co-citation analysis, Piezos, Web of Science

1. Introduction

In 2013, Ardem Patapoutian discovered Piezo, the pressure-sensitive ion channel family. They are present in several extinct species and have profound evolutionary roots. Patapoutian confirmed that Piezos are essential genes for pressure perception in mammals. His research shows that Piezos can form ion channels, which are directly responsible for Merkel cells and tactile terminals in the skin, and the pressure sensing of proprioceptors.^[1] Since its discovery, mechanosensitive ion channels have garnered extensive attention from both domestic and international researchers, particularly the Piezo channel, which was discovered in recent years and is crucial for mammalian mechanical signal transduction. This channel is widely distributed and is involved in various physiological and pathological

processes in the body. Piezos are mechanically sensitive ion channels that play a significant role in physiological processes such as touch, autonomous regulation of blood pressure, vascular development, and disease processes such as cell adhesion, tumor cell proliferation, migration, and differentiation.^[2] This research used the Citespace software developed by Professor Chen Chaomei’s team to conduct bibliometrics analysis. Bibliometrics research helps us comprehend the past and future of this field, as well as intuitively uncover the dynamic evolution process and current state. At the same time, it is possible to categorize the authors, institutions, and funding status of this field’s research. This study conducts a bibliometric analysis of the research on Piezos, assesses the overall situation of the research on Piezos, and proposes areas for further investigation.

SL, BS, NJ, CP and XR contributed equally to this work.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

The authors have no ethical statement to disclose.

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2. Methods

2.1. Data source

The research data was retrieved from the Web of Science (WoS) core collection, which is the leading and the most reliable worldwide research resource. The selected data includes all reputable English original articles. The search term was set to TS = (“Piezo1” OR “Piezo2”). The time interval was established from January 1, 2010 to October 8, 2021.

2.2. Data processing and methodology

CiteSpace (version: 5.6. R5) is a visual analysis software based on the Java platform. It was developed by Professor Chen Chaomei’s team from Drexel University. With a combination of information visualization, graphics, metrology, and other disciplines, CiteSpace can visually demonstrate the knowledge structure of a particular study topic. CiteSpace uses data of the textual format from WoS, preprocesses the data and then imports it into Excel for analysis and column mapping. The literature data was then loaded into CiteSpace (version 5.6. R2) and analyzed visually, including journal co-citation analysis, author co-citation analysis, country co-citation analysis and keyword co-citation analysis.^[3] The parameters of CiteSpace were set as follows: The time frame was established from 2010 to 2021, and the data was analyzed one year at a time, since the development trend in this subject can be discerned through yearly study. “Title”, “Abstract”, “Keyword Plus”, “Author Keywords” were key parameters to be examined to identify research trends.

3. Results

3.1. Research performance

The number of articles published has increased gradually during the previous decade. In 2018, more than one hundred pieces were published for the first time. In 2021, 185 articles have been published. As of October 8, 2021, 902 articles have been published. As shown in Figure 1, the histogram represents the number of posts issued each year, and the yellow dashed line represents the cumulative volume of posts.

3.2. Funding agency

The funding of fund projects is crucial to the advancement of this discipline. The current state and future of this field may be determined by the fund’s origin and financing. The

bibliometric results showed that the most funded institutions are National Institutes of Health (NIH) USA, and the United States Department of Health Human Services, which both supported 256 articles, accounting for 56.76% of the total literature. The National Natural Science Foundation of China (NSFC) came in second, funding 93 articles, accounting for 10.31% of the total. The top ten funding organizations are shown in Table 1.

3.3. Analysis of authors and author collaboration

The number of articles published by the author is indicative of the depth and breadth of their study in this topic. The more papers the author has published, the longer time he or she has devoted to research, and correspondingly he or she has achieved certain progress. One may even argue that the author with the most published articles leads the development trend of the field. The findings of this study showed that the author with the most posts is Ardem Patapoutian, with a total of 28 posts, followed by Frederick Sachs and Bailong Xiao, with 17 and 15 posts respectively, and the top ten are shown in Table 2. Figure 2 demonstrates that the collaboration between the authors is relatively close. The collaboration partnerships can be categorized into two groups.

3.4. Distribution of countries/regions and institutions

902 papers were published by 52 nations and 276 institutions. As shown in Table 3, the United States (254, 28.16%) and China (120, 13.30%) produced the greatest number of publications, which were more than twice as numerous as those from all other countries. The United States is home to eight out of the top 10 institutions. In addition, several other countries and institutions, such as China (0.07) demonstrated a high degree of centrality, as indicated by the purple circles in Figures 3 and 4. Each circle in the Figure 3 represents a country, and its size indicates the number of publications produced by that nation. The lines connecting the circles denote international cooperation, and the thicker the lines, the closer the cooperation. Overall, there is active interaction between nations and institutions.

3.5. Co-occurrence of keywords

We used CiteSpace software to generate a co-occurrence map of keywords (Fig. 5). Table 4 is a listing of the top 20 most often used. Keywords constitute the core of an article. By

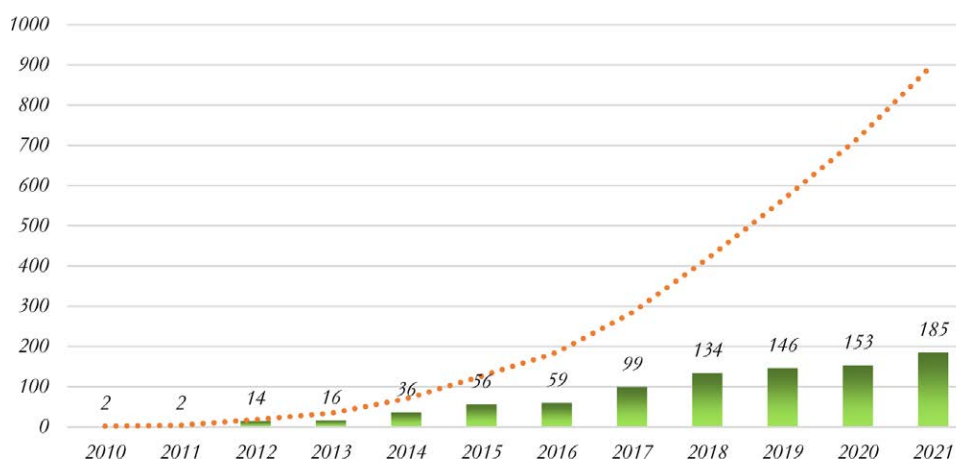


Figure 1. Time sequence of relevant papers on Piezos published from 2010 to 2021 in Web of Science.

Table 1

Funding agency of relevant papers on Piezos published from 2010 to 2021 in Web of Science.

No.	Funding agency	Record	% of 902
1	National Institutes of Health NIH USA	256	28.381
2	United States Department of Health Human Services	256	28.381
3	National Natural Science Foundation of China NSFC	93	10.31
4	European Commission	86	9.534
5	NIH National Institute of Neurological Disorders Stroke NINDS	63	6.984
6	UK Research Innovation UK RI	44	4.878
7	NIH National Institute of General Medical Sciences NIGMS	41	4.545
8	NIH National Heart Lung Blood Institute NHLBI	40	4.435
9	NIH National Institute of Dental Craniofacial Research NIDCR	40	4.435
10	Medical Research Council UK MRC	39	4.324

Table 2

Top 10 authors in the number of papers published.

No	Freq	Degree	Centrality	Author	Year	Half-Life
1	28	30	0.13	Ardem Patapoutian	2010	5.5
2	17	13	0.06	Frederick Sachs	2011	3.5
3	15	15	0.02	Bailong Xiao	2012	6.5
4	12	22	0.01	Bertrand Coste	2010	3.5
5	11	9	0.02	Philip A Gottlieb	2011	4.5
6	11	28	0.05	Adrienne E Dubin	2010	4.5
7	10	3	0	Jianguo G Gu	2012	3.5
8	10	24	0.01	Jayani Mathur	2010	3.5
9	9	11	0.04	Boris Martnac	2016	3.5
10	9	9	0	David J Beech	2018	1.5

CiteSpace, v. 5.8.R1 (64-bit)
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 Timespan: 2010-2021 (Slice Length=1)
 Selection Criteria: q=0.25, LRF=3.0, L/N=10, LBY=5, e=1.0
 Network: N=320, E=721 (Density=0.0141)
 Largest CC: 117 (36%)
 Nodes Labeled: 1.0%
 Pruning: Pathfinder

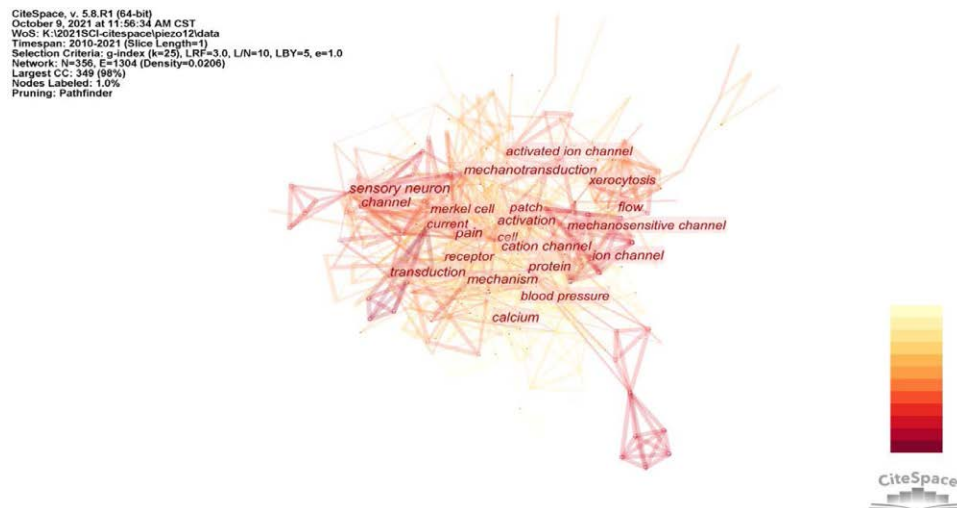
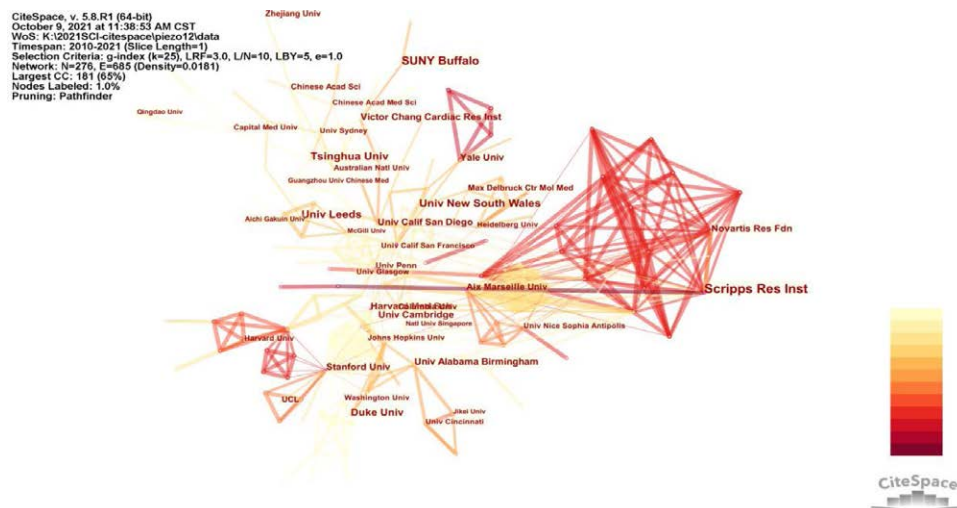
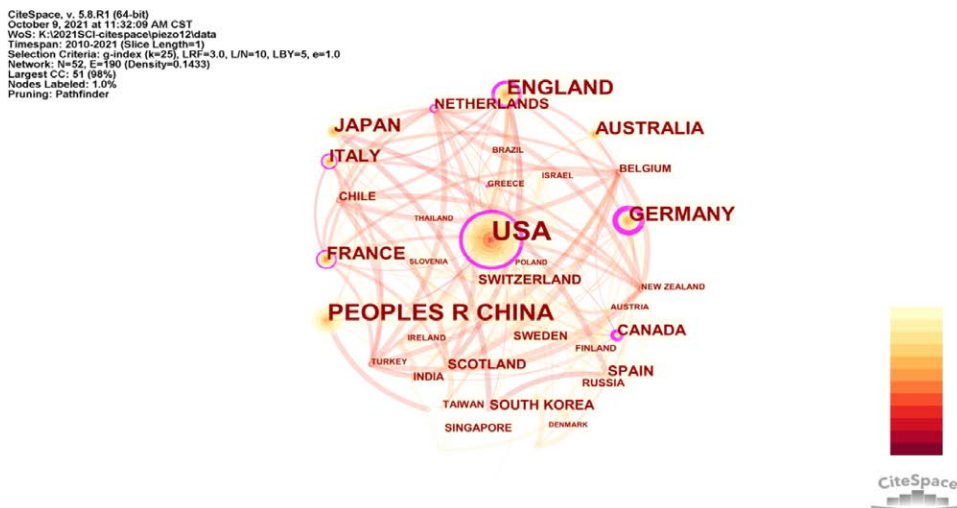


Figure 2. Map of authors' collaborations related to Piezos research.

Table 3

Top 10 countries/regions and institutions related to pyroptosis.

Rank	Country	Year	Centrality	Count (%)	Institution	Year	Centrality	Count (%)
1	USA	2010	0.29	254 (28.16%)	Scripps Res Inst	2010	0.15	28 (3.10%)
2	People R China	2012	0.08	120 (13.30%)	SUNY Buffalo	2011	0.01	20 (2.22%)
3	England	2012	0.29	65 (7.21%)	Tsinghua Univ	2017	0.07	17 (1.88%)
4	Germany	2014	0.46	57 (6.32%)	Univ New South Wales	2017	0.03	16 (1.77%)
5	Japan	2013	0.05	46 (5.10%)	Univ Leeds	2018	0.04	16 (1.77%)
6	France	2013	0.15	40 (4.43%)	Duke Univ	2014	0	13 (1.44%)
7	Australia	2014	0.06	39 (4.32%)	Victor Chang Cardiac Res Inst	2016	0.05	12 (1.33%)
8	Italy	2013	0.15	29 (3.22%)	Univ Calif San Diego	2012	0.09	12 (1.33%)
9	Canada	2012	0.24	19 (2.11%)	Stanford Univ	2013	0.14	12 (1.33%)
10	Spain	2013	0.06	18 (2.00%)	Novartis Res Fdn	2012	0.06	11 (1.22%)



analyzing the keywords, we are able to summarize the study topics in a specific field and investigate research hotspots and directions. According to Table 4, excluding piezo1 and piezo2, the most often used keywords in this study are “mechanotransduction”, “ion channel”, “mutation”, “channel”, “mechanism”, “expression”, “cell”, “touch”, “protein”, and “merkel cell”, indicating that these fields were the focus of research on Piezo.

The literature represented by the co-citation network was clustered into 11 categories: #0 “piezo2”, #1 “endothelial cell”, #2 “xerocytosis”, #3 “current”, #4 “calcium”, #5 “mutation”, #6 “activated ion channel”, #7 “ca²⁺ influx”, #8 “protein”, #9 “smooth muscle”, and #10 “nociception” (Fig. 6 and Table 5). The modularity value was 0.5282, indicating that the specialties were distinctly characterized in terms of co-citation clusters. The average Silhouette score

Table 4
Top 20 keywords related to Piezos.

No.	Freq	Degree	Centrality	Keyword	No.	Freq	Degree	Centrality	Keyword
1	134	14	0.04	Piezo1	11	50	25	0.23	Protein
2	101	25	0.07	Mechanotransduction	12	45	20	0.06	Merkel cell
3	96	16	0.04	Piezo2	13	42	10	0.02	Architecture
4	80	24	0.09	Ion channel	14	41	26	0.12	Activation
5	80	18	0.07	Mutation	15	39	22	0.1	Activated ion channel
6	71	23	0.06	Channel	16	37	22	0.09	Receptor
7	69	24	0.09	Mechanism	17	32	26	0.09	Transduction
8	60	16	0.04	Expression	18	30	28	0.1	Pain
9	58	20	0.05	Cell	19	28	15	0.03	Pressure
10	53	7	0	Touch	20	28	30	0.12	Sensory neuron

CiteSpace, v. 5.8.R1 (64-bit)
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 Selection Criteria: g-index (k=25), LRF=3.0, L/N=10, LBY=5, e=1.0
 Network: N=358, E=1304 (Density=0.0206)
 Largest CC: 349 (98%)
 Nodes Labeled: 1.0%
 Pruning: Pathfinder
 Modularity Q=0.5282
 Weighted Mean Silhouette S=0.7706
 Harmonic Mean(Q, S)=0.6268

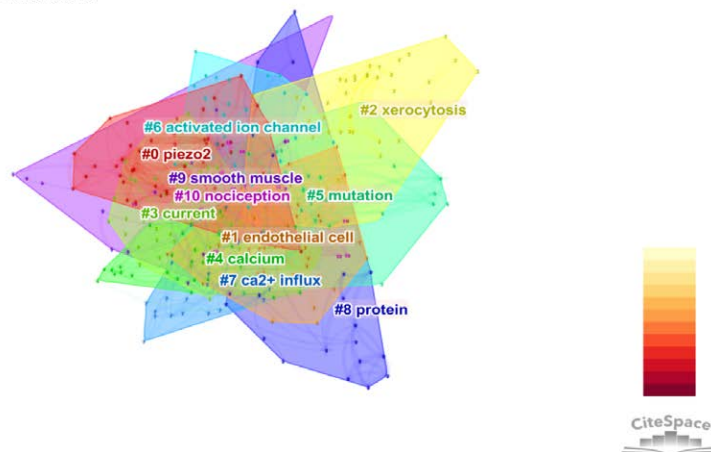


Figure 6. The term co-occurrence network in Piezos research.

Table 5
Top 11 subjects of cluster analysis.

Cluster ID	Size	Centrality	Year	Cluster label (LLR)
#0	49	0.807	2014	Mechanotransduction; touch; activated ion channel; distal arthrogyposis; identification piezo2; channel; merkel cell; transduction; mechanoreceptor
#1	45	0.709	2018	Ion channel; mc3t3-e1 cells; canalicular pressure; malignant transformation; tissue stiffness shear stress; endothelial cells; mc3t3-e1 cells; canalicular pressure; malignant transformation
#2	42	0.764	2016	Piezo1 gene; hereditary xerocytosis; next-generation sequencing; molecular modeling; ionic channels protein stomatocytosis; splenectomy; anemia; band 3 deficiency; spherocytosis
#3	38	0.77	2014	Current; piezo2; merkel cell; transduction; mechanoreceptor touch; neuron; stretch; piezo1; identification
#4	36	0.609	2017	Pressure; mechanotransduction; channel; stretch; urinary bladder mechanism; release; mutation; calcium; human erythroblast
#5	34	0.82	2015	Mutation; architecture; activated ion channel; protein; mechanosensitive channel ion channel; reconstitution; red blood cells; adaptation; calmodulin
#6	30	0.77	2017	Activated ion channel; mechanotransduction; touch; stretch; merkel cell mutation; membrane; patch; mechanosensitivity; piezo1
#7	21	0.816	2019	Innate immunity; channel; Ca ²⁺ influx; complex; yap/taz adaptation; model; drg neuron; mechanoreceptor; inactivation
#8	20	0.897	2015	Protein; ion channel; mammalian inner ear; transduction; conductance mechanotransduction; piezo2; movement; fusimotor drive; gait
#9	17	0.809	2015	Piezo2; piezo1; yoda1; mechano-nociception; trpv1 gene; channel; paradoxical component; protein; Ca ²⁺
#10	17	0.846	2016	Piezo1; piezo2; trpv1; mechanically gated channel; pain expression; stiffness; outgrowth; extension; rigidity

was 0.7706. Keywords from the cited publications were assigned to the categories. Through a thorough analysis of the tags and articles related to each category of nodes, the fundamental conceptual structure and the current state of research in Piezo can be determined. The Piezo can be identified from the list of references that had strong citation bursts from 2010 to 2021 (Table 6). It shows that cluster “current” has the longest research duration. Current research emphasis is on “gene expression”.

Figure 7 is a timeline diagram depicting the temporal evolution of these topics. The publication dates of papers were displayed on the top, while the most recent articles were displayed on the right. The vertical line indicated distinct clusters. The number of nodes in the cluster reflected the importance of this topic in the field. The greater the number of nodes, the greater its significance. This timeline view illustrated the development, popularity and decline of research topics. As depicted in Figure 7, #3 “current” and #8 “protein” emerged first, and #7 “ca²⁺ influx” and #9 “smooth muscle” developed at a later stage.

3.6. Co-citation of reference

The top 20 most cited articles on Piezo are shown in Table 7 and Figure 8. The first 10 articles are all original works. Only one of these 20 articles is a review: “Touch, Tension, and Transduction - The Function and Regulation of Piezo Ion Channels”. In Table 7, we illustrated the main conclusion of each article.^[4-23]

3.7. Journals and co-cited journals

There are 237 academic journals that have published articles on ferroptosis research. The top 10 active journals published 258 articles, representing 28.602% of the total number of publications. Figure 9 depicts the top 20 journals. Figure 10 presents a dual-map overlay of the number of publications with reference to the focus of the journals. The labels on the map represent the many research subjects covered by all the journals, allowing the overall visualization to illustrate patterns in the scientific portfolio. The left half of the map indicates the citing journals, whereas the right half represents the cited journals. The width of the connecting paths is proportional to the frequency of z-score-scale citation. Overall, there was one main citation path on the current map. It is Molecular Biology of the Cell.

4. Conclusion

Ardem Patapoutian has been a researcher at the Howard Hughes Medical Institute since 2014. The capacity to perceive heat, cold, and touch is vital to human survival and supports our interaction with the environment. We take these sensations for granted in daily life, but how are nerve impulses generated so that we can perceive temperature and pressure? The recipient of this year’s Nobel Prize solved this problem. In 2010, Coste et al found the Piezo channel, a novel form of mechanosensitive cation channel in mouse neuroblastoma cell lines. It consists of a central ion channel structure and a three-lobed propeller-like mechanoreceptor structure with two subtypes: Piezo1 and Piezo2 protein.^[4]

Table 6

Top 10 keywords with the strongest citation bursts.

Keywords	Year	Strength	Begin	End	2010-2021
Current	2010	2.67	2010	2016	████████████████████
Sensory neuron	2010	8.58	2012	2017	████████████████████
Protein	2010	3.25	2013	2014	████████████████████
Mechanical channel	2010	2.87	2013	2015	████████████████████
Hair cell	2010	3.06	2014	2016	████████████████████
Merkel cell	2010	2.81	2014	2016	████████████████████
Mice	2010	3.49	2015	2018	████████████████████
Distal arthrogryposis	2010	3.19	2015	2017	████████████████████
Gene	2010	3.57	2017	2018	████████████████████
Gene expression	2010	2.95	2019	2021	████████████████████

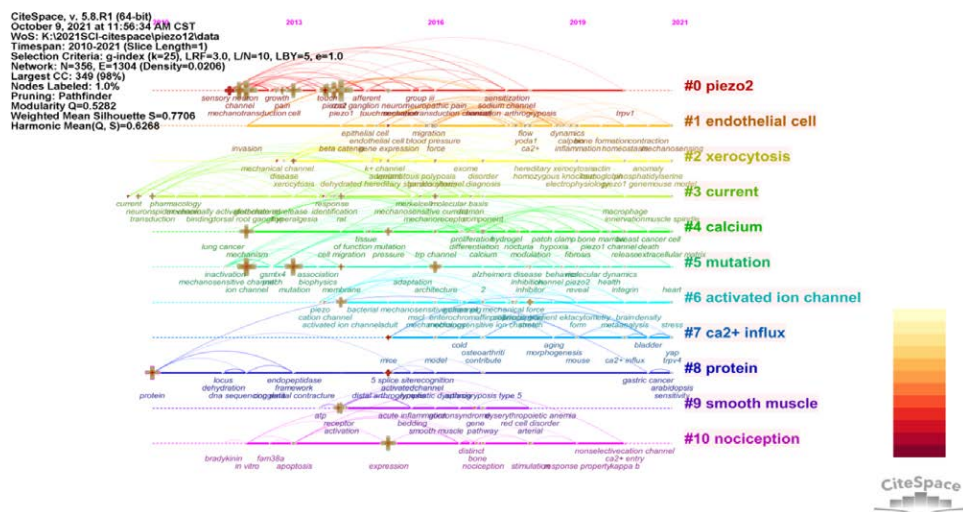


Figure 7. Timeline viewer related to Piezos.

Table 7
The top 20 PIEZO articles with the most citations (up to October 8, 2021).

NO.	Freq	Degree	Centrality	Author	Year	DOI	Main conclusion
1	107	3	0	Ranade SS[]	2014	10.1038/nature13980	Most rapidly adapting, mechanically activated currents in dorsal root ganglion neuronal cultures are absent in Piezo2 conditional knockout mice, and ex vivo skin nerve preparation studies show that the mechanosensitivity of low-threshold mechanoreceptors strongly depends on Piezo2.
2	101	8	0.02	Woo SH[]	2014	10.1038/nature13251	Piezo2 is the Merkel-cell mechanotransduction channel and provide the first line of evidence that Piezo channels have a physiological role in mechanosensation in mammals.
3	100	11	0.05	Li J[]	2014	10.1038/nature13701	Piezo1 channels function as pivotal integrators in vascular biology.
4	86	14	0.05	Ranade SS[]	2014	10.1073/pnas.1409233111	Piezo1 is activated by shear stress, the major type of mechanical force experienced by endothelial cells in response to blood flow.
5	82	10	0.03	Woo SH[]	2015	10.1038/nn.4162	The mechanically activated nonselective cation channel Piezo2 was expressed in sensory endings of proprioceptors innervating muscle spindles and Golgi tendon organs in mice.
6	81	9	0.02	Cahalan SM[]	2015	10.7554/eLife.07370	Mechanically activated Piezo1 plays an essential role in RBC volume homeostasis.
7	81	7	0.03	Syeda R[]	2015	10.7554/eLife.07369	Piezo1 is amenable to chemical activation and raise the possibility that endogenous Piezo1 agonists might exist.
8	76	12	0.03	Coste B[]	2012	10.1038/nature10812	Piezo proteins are an evolutionarily conserved ion channel family involved in mechanotransduction.
9	73	11	0.04	Cox CD[]	2016	10.1038/ncomms10366	PIEZO1 channels must sense force directly transmitted through the bilayer.
10	73	9	0.03	Wang SP[]	2016	10.1172/JCI87343	The PIEZO1 activator Yoda1 mimicked the effect of fluid shear stress on endothelial cells and induced vasorelaxation in a PIEZO1-dependent manner.
11	70	6	0.01	Wu J[]	2017	10.1016/j.tibs.2016.09.004	Piezos as ion channels that sense light touch, proprioception, and vascular blood flow, ruled out roles for Piezos in several other mechanotransduction processes, and revealed the basic structural and functional properties of the channel.
12	69	3	0.01	Sao-tome K[]	2018	10.1038/nature25453	A high-resolution cryo-electron microscopy structure of the mouse Piezo1 trimer. The detergent-solubilized complex adopts a three-bladed propeller shape with a curved transmembrane region containing at least 26 transmembrane helices per protomer. The flexible propeller blades can adopt distinct conformations, and consist of a series of four-transmembrane helical bundles that we term Piezo repeats. Carboxy-terminal domains line the central ion pore, and the channel is closed by constrictions in the cytosol. A kinked helical beam and anchor domain link the Piezo repeats to the pore, and are poised to control gating allosterically. The structure provides a foundation to dissect further how Piezo channels are regulated by mechanical force.
13	68	8	0.02	Ge JP[]	2015	10.1038/nature15247	Piezo1 may use its peripheral regions as force sensors to gate the central ion-conducting pore.
14	67	9	0.01	Syeda R[]	2016	10.1016/j.cellrep.2016.10.033	Mechanical perturbations of the lipid bilayer alone are sufficient to activate Piezo channels, illustrating their innate ability as molecular force transducers.
15	65	10	0.04	Gudipaty SA[]	2017	10.1038/nature21407	Mammalian epithelial cell division occurs in regions of low cell density where cells are stretched, mechanical stretch itself rapidly stimulates cell division through activation of the Piezo1 channel.
16	63	8	0.02	Zhao QC[]	2018	10.1038/nature25743	Piezo1 possesses a unique 38-transmembrane-helix topology and designated mechanotransduction components, which enable a lever-like mechanogating mechanism.
17	60	20	0.06	Coste B[]	2010	10.1126/science.1193270	Piezos are components of MA cation channels.
18	59	12	0.02	Bae C[]	2013	10.1073/pnas.1219777110	In addition to the behavior of individual channels, groups of hPIEZO1 channels could undergo simultaneous changes in kinetics including a loss of inactivation and a long (~200 ms), silent latency for activation. hPIEZO1 exists in spatial domains whose global properties can modify channel gating. The mutations that create HX affect cation fluxes in two ways: slow inactivation increases the cation flux, and the latency decreases it.
19	58	13	0.05	Lewis AH[]	2015	10.7554/eLife.12088	Piezo1 responds to lateral membrane tension with exquisite sensitivity as compared to other mechanically activated channels and that resting tension can drive channel inactivation, thereby tuning overall mechanical sensitivity of Piezo1.
20	56	14	0.04	Maksimovic S[]	2014	10.1038/nature13980	A single ion channel that displays rapidly adapting, mechanically activated currents in vitro is responsible for the mechanosensitivity of most low-threshold mechanoreceptor subtypes involved in innocuous touch sensation. touch and pain sensation are separable, suggesting that as-yet-unknown mechanically activated ion channel(s) must account for noxious (painful) mechanosensation.

The most significant cluster result is #0 “Piezo2”, which is one of two Piezo proteins identified in humans and other mammals. It involves molecular, cellular, and system level work.^[4] Endothelial cell, activated ion channel, Ca²⁺ influx, and smooth muscle etc indicate that Piezos can generate ion channels, and they are directly responsible for skin Merkel cells, tactile terminals, and the pressure sensing of proprioceptors. At the same time, Piezos can simultaneously sense pressure through the

nerve endings of blood vessels and lungs, influence the number of red blood cells and blood vessel physiology, and produce a range of inherited human disorders. The discovery of Piezos paved the way for the growing area of mechanobiology, an emerging scientific field that combines biology, engineering, and physics. It examines how the physical forces and mechanical properties of cells and tissues affect health and illness, as well as their effects.

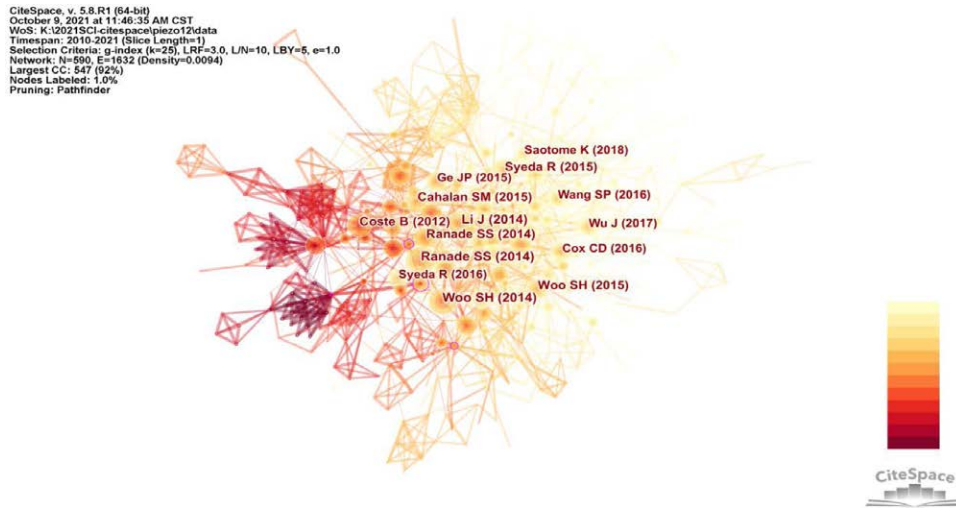


Figure 8. Document co-citation analysis in Piezos research.



Figure 9. The top 20 journals according to cited records in the field.

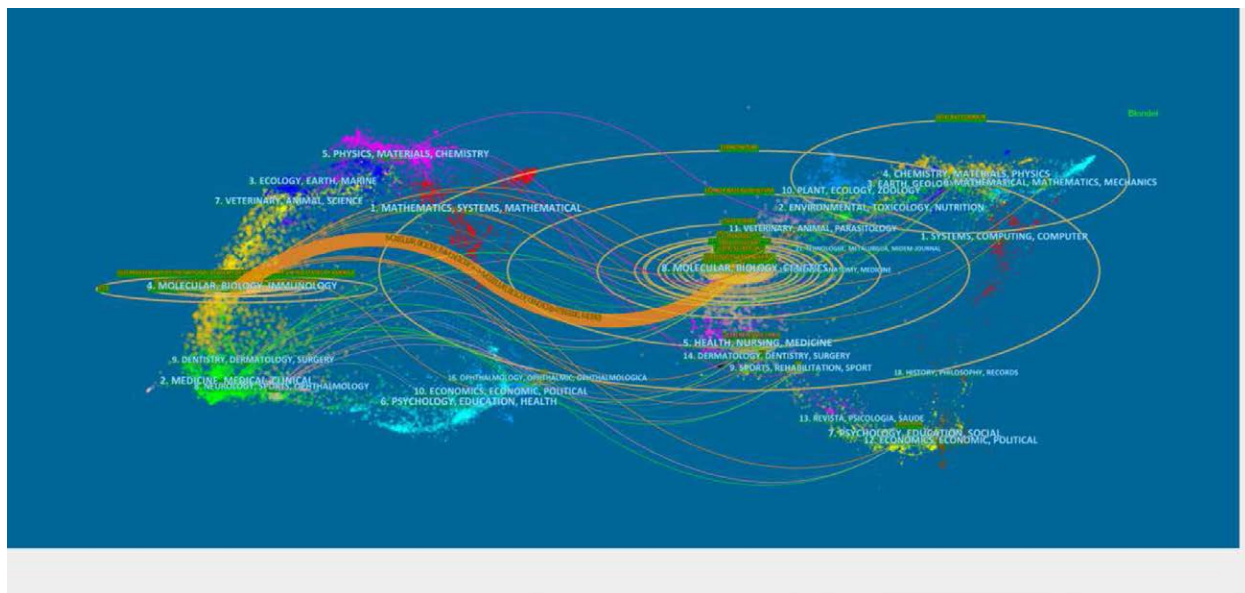


Figure 10. A dual-map overlay of the journals on Piezos research generated by using CiteSpace software.

In conclusion, this study provides an overview of the evolution and current global research directions of Piezos.

Author contributions

Conceptualization: Ciming Pan, Shuai Li.

Data curation: Banglong Song.

Funding acquisition: Nan Jiang.

Investigation: Qianqian Dai.

Methodology: Quangen Chu, Xue Ren.

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