Knowledge mapping of research on the mitochondrial unfolded protein response: a bibliometric and visual analysis

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Background: The mitochondrial unfolded protein response (UPR^{mt}) is a mitochondria stress response, which exerts a crucial role in maintaining mitochondrial proteostasis during stress. However, there is no bibliometric analyses systematically studied this field which could comprehensively review research trends, evaluate publication performances and provide future perspectives.

Methods: Articles investigating UPR^{mt} published between 1994 and 2021 were downloaded from the Core Collection of the Web of Science (WOS). CiteSpace and VOSviewer bibliometric software were applied for bibliometric and visual analyses.

Results: A total of 2,073 papers researching UPR^{mt} were retrieved. According to the published number of papers, the field of UPR^{mt} research has gone through its infancy (after 2000) and rapid growth (after 2021) phases. The United States and China contributed the most to UPR^{mt} research. Regarding the distribution of institutions, Harvard University was the most influential institution. The most prolific authors are Johan Auwerx and CM Haynes. *PLoS One* is the most extensive journal in the field of UPR^{mt} research, while the *Cell Death and Differentiation* journal had the greatest impact among the most-authored journals. Moreover, biochemistry/molecular biology, and cell biology are the largest subject areas. UPR^{mt} research is mainly categorized as UPR^{mt}, transcription, endoplasmic reticulum (ER) stress, lipotoxicity, mitophagy, inflammation, skeletal muscle, hypoxia, apoptosis, mitochondrial dysfunction, neurodegeneration, mitochondrial permeability transition, and integrated stress response.

Conclusions: At present, research on UPR^{mt} is booming. Further strengthening the cooperation and exchanges between countries, institutions, and authors in the future will surely promote the development of this field.

Keywords: Mitochondrial unfolded protein response (UPR^{mt}); bibliometric analysis; Web of Science (WOS); CiteSpace; VOSviewer

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Introduction

Mitochondria are double-membrane organelles that are present in nearly all eukaryotic cells and represent the first line of defense during stress, which triggers mitochondrial dysfunction (1). Mitochondrial function primarily mediates various cellular processes, including Adenosine

Triphosphate (ATP) production; metabolism of nucleotides, amino acids, and lipids; Ca^{2+} buffering; modulation of cell deaths; etc. (2-4). Eukaryotic cells must accurately monitor the integrity of the mitochondrial network to overcome environmental damage and respond to physiological cues (5-7). The import, folding, and quality control of the mitochondrial proteome encompassing over 1,000 proteins encoded by mitochondrial and nuclear genomes are adjusted by transcriptional programming, a mitochondrial stress response process known as the mitochondrial unfolded protein response (UPR^{mt}) (8-10). UPR^{mt} alleviates the abnormal protein accumulation in mitochondria by normalizing mitochondrial protein folding and degradation through initiating the transcriptional activation programming of mitochondrial chaperones and proteases, thereby protecting cells from broad mitochondrial stress (11-13). Mitochondrial chaperones are capable of helping misfolded proteins return to their normal conformation, and aid newly synthesized proteins in folding accurately, while proteases are capable of degrading useless proteins (14-16). Recent research has revealed that UPRs^{mt} are involved in maintaining stem cell homeostasis, promoting tissue regeneration, and prolonging lifespan (17). Losing UPR^{mt} components has a profound effect on cell proliferation, by activating UPR^{mt} components, hematopoietic stem cells (HSCs) can transit from quiescence to proliferation (17). Additionally, UPR^{mt} plays a role in dedifferentiating cells and obtaining stem cell-like properties during tissue remodeling (18). Accumulated evidence suggests that abnormal UPR^{mt} contributes to a variety of diseases, including congenital diseases (19), cancers (20), and neurodegenerative diseases (21). Thus, an in-depth study of the UPR^{mt} may assist in understanding its roles in the progression and clinical outcomes of human diseases and offer novel insights into clinical prevention and therapy.

Firstly, developed by American bibliologists in 1969, bibliometric analysis is a method of applying mathematical and statistical approaches to study articles, reviews, etc. (22). According to the features of literature databases and bibliometrics, bibliometric analysis is capable of evaluating the distribution of countries/regions, institutions, authors, etc. in a specific research field, thereby laying a foundation for future research directions and development (23). Moreover, this analytical method is capable of qualitatively and quantitatively evaluating research trends and helping scholars to quickly master the research hotspots and development tendencies of a specific research area (24). However, to the best of our knowledge, there have been no bibliometric analyses systematically studied this UPR^{mt} field. In this study, we utilized CiteSpace (Philadelphia, PA, USA) and VOSviewer software (Leiden University, Leiden, The Netherlands) to systematically and visually analyze the UPR^{mt} research area and probe the status of current research. Our study objectively revealed the research tendencies, accurately evaluated the research progress on the UPR^{mt}, and provided a reference for combining the research framework and developing novel insights into the research area.

Highlight box

Key findings

- This study used bibliometric analyses systematically studied mitochondrial unfolded protein response (UPR^{mt}) field, presents a knowledge mapping of research on the UPR^{mt}.

What is known and what is new?

- UPR^{mt} exerts a crucial role in maintaining mitochondrial proteostasis during stress. At present, research on the UPR^{mt} is booming.
- Our study objectively revealed the tendency, accurately evaluated the research progress on UPR^{mt}, and provided a reference for combining the research framework and developing novel insights into UPR^{mt} research.

What are the implications, and what should change now?

- Further strengthening of the cooperation and exchanges between countries, institutions, and authors in the future will surely promote the development of UPR^{mt} field.

Methods

Data collection

The Web of Science (WOS) Citation database is an information retrieval platform developed by Thomson Reuters, comprising over 9,000 authoritative and influential academic journals. Literature on the UPR^{mt} was downloaded from the Core Collection of the WOS (http://apps.webofknowledge.com), using "mitochondrial unfolded protein response" as the subject heading, "article" and "review" as the literature types, "English" as the language, and 1900–2021 as the period. This literature search was carried out on August 25, 2021. A total of 2,073 relevant papers were retrieved. The deduplication function of CiteSpace software was implemented to inspect whether there were any duplicate articles, and no duplicates were found.

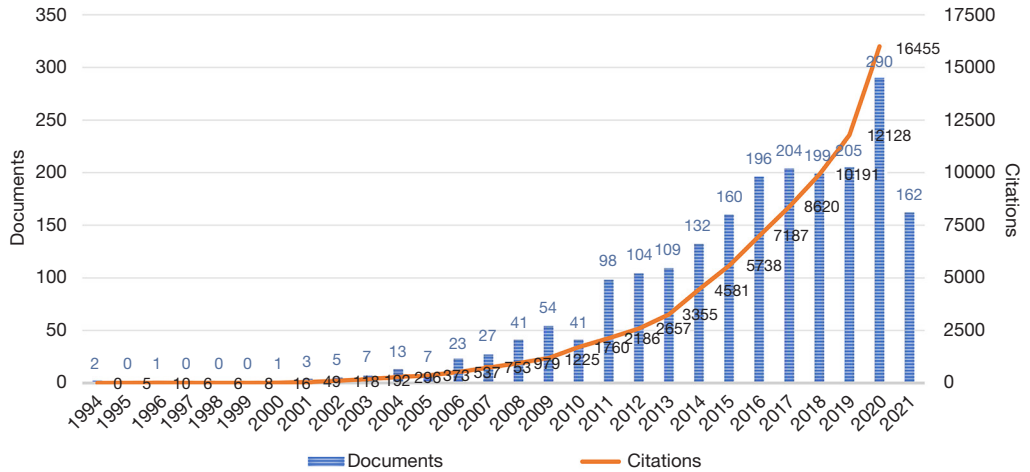


Figure 1 Number and citations of published papers in the UPR^{mt} research area [1994–2021]. The blue histogram represents the number of publications; and the orange curve represents the citations of published papers. UPR^{mt}, mitochondrial unfolded protein response.

Methodology

This study applied bibliometric approaches and knowledge graph visualization software to present the knowledge distribution and increasing tendency of UPR^{mt} research from distinct perspectives. Proposed by Pritchard, bibliometric analysis is capable of revealing the study features of a specific research area with quantitative and statistical approaches; it is a critical study tool that has been utilized in a variety of research areas. The knowledge graph represents a crucial step in bibliometrics, objectively presenting the research status of a specific discipline. A few visualization software programs have been developed to perform bibliometrics analyses.

In this study, we applied CiteSpace (version 5.5.R2; https://sourceforge.net/projects/citespace) (25-27) and VOSviewer (version 1.6.16; https://www.vosviewer.com) software (28-30) to visualize bibliometric analysis results. Developed by Eck and Waltman, VOSviewer is an efficient co-occurrence analysis and co-citation analysis visualization software, which was applied to display national, institutional, and author collaboration networks. CiteSpace is a powerful user-friendly information visualization software that was proposed by Professor Chen Chaomei; it is an open JAVA application employed to visualize and analyze the tendency and status of scientific papers. CiteSpace software can be applied for the knowledge mapping of countries, institutions, journals, research areas, authors, co-citation clustering, as well as highly frequent keyword clustering.

Statistical analysis

This study mainly used quantity and percentage to describe the indicators statistically. There was no difference analysis involved, and there was no need to set a test level.

Results

Distribution and trends in the number and citations of published papers in the UPR^{mt} research area

Figure 1 depicts the number of papers on UPR^{mt} and their citations. The first literature in this field was published by Nguyen *et al.* in 1994: "*Increased thermal aggregation of proteins in ATP-depleted mammalian cells*" (31). In the early stages of this field, the number of papers was relatively small but the overall trend has been increasing. We can regard 2000 and 2010 as two important time points for the number of published papers. The UPR^{mt} was initially noticed by scientific researchers after 2000; however, since 2010, the number of published papers has significantly increased. This indicates that the output of academic achievements in this field is gradually increasing and research on UPR^{mt} is entering an active period. Papers in this field have been cited 91,137 times, and the H index is 132. The orange curve in *Figure 1* represents the citations, and its slope exhibits a gradually increasing trend, showing a "J" shape. According to our analysis of the number and citations of published papers, the popularity of the UPR^{mt} field is

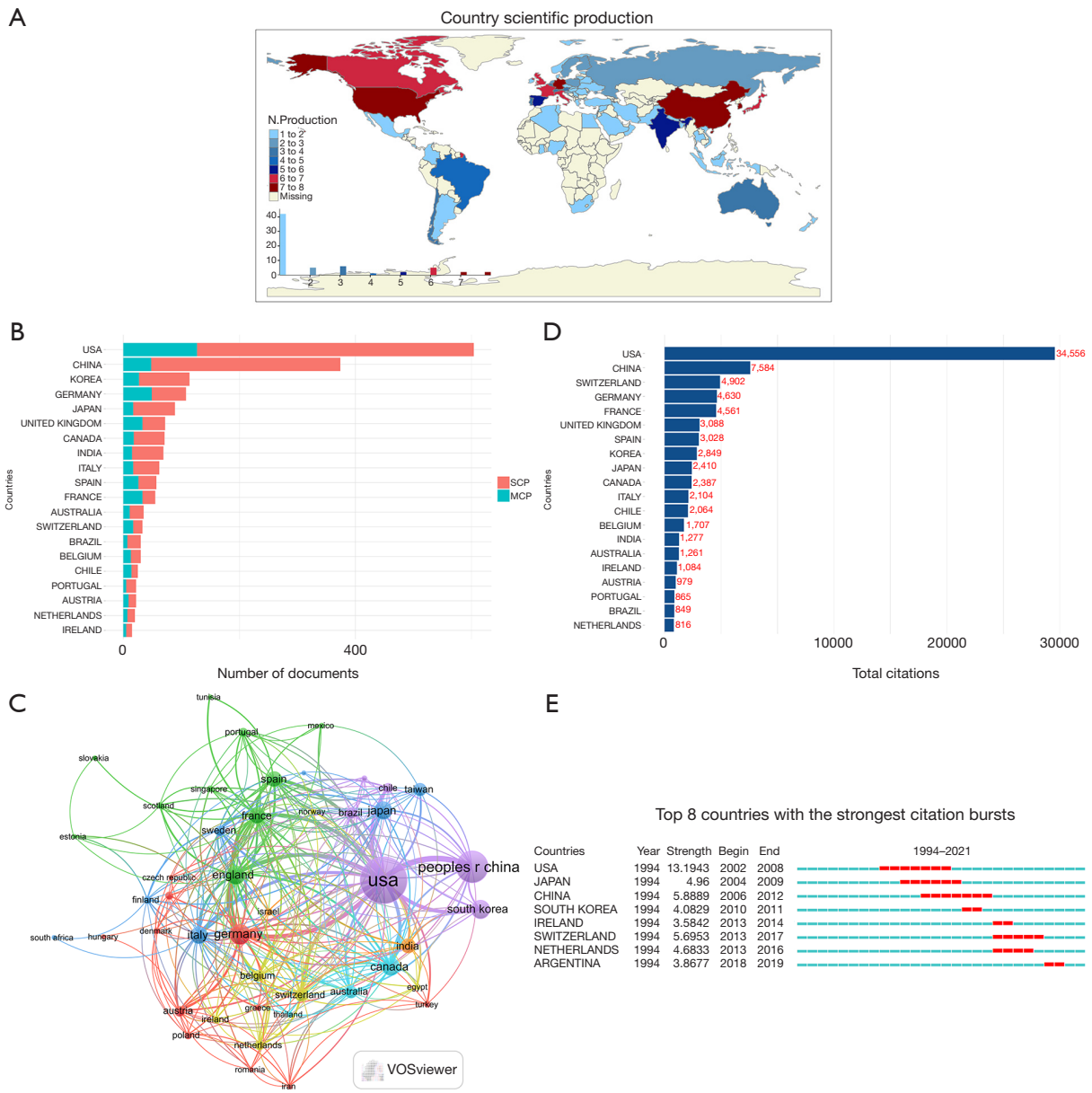


Figure 2 Analysis of the countries/regions in the UPR^mt research area. (A) World map of the total country scientific output [2006–2021]. (B) Distribution of SCP and MCP of published papers in the top 20 countries [2006–2021]. (C) The national/regional cooperation network. (D) The citations of published papers in the top 20 countries [1994–2021]. (E) The top eight countries with the strongest citation bursts [1994–2021], the red part represents the year that emerges, i.e., the period in which the citations of papers in that country/region changed significantly (each bar represents a single year). UPR^mt, mitochondrial unfolded protein response; SCP, single-country publications; MCP, multiple-country publications.

increasing every year, and it has great research potential.

Analysis of countries/regions in the UPR^mt research area

Currently, researchers from 71 countries/regions have published papers on the UPR^mt (*Figure 2A*). Research in this field has mainly been performed in North America, East Asia, and Europe. Among these regions, researchers in the United States have published a total of 779 papers, ranking first and accounting for 37.627% of the total

Table 1 The top 10 countries/regions according to the number of publications in the UPR^{mt} research area [1994–2021]

Rank	Country	Publications (n)	Proportion (%)	Citations	Co-occurrence frequency
1	USA	779	37.627	43,776	421
2	China	355	17.125	7,357	110
3	Germany	149	7.188	6,879	150
4	South Korea	123	5.933	3,223	52
5	UK	121	5.933	5,463	145
6	Japan	114	5.548	3,780	58
7	Canada	112	5.403	5,378	95
8	Italy	100	4.824	6,819	91
9	France	93	4.486	8,588	126
10	Spain	80	3.859	4,501	80

UPR^{mt}, mitochondrial unfolded protein response.

published research. China ranks second, with 355 published papers, accounting for 17.125% of the total literature. As shown in *Table 1*, there is a large gap between the number of published articles from the United States and China and those from other countries. Moreover, the United States leads in both single-country publications (SCP) and multiple-country publications (MCP), followed by China (*Figure 2B*).

Using VOSviewer software, we mapped the national/regional cooperation network and the result is shown in *Figure 2C*. Each node represents a country/region, and the size of the node reflects the number of publications in that country/region. Chinese researchers cooperate more with scholars from the United States, South Korea, Brazil, and other countries, but do not belong to the same cooperation network as other countries with relatively high numbers of published literature (such as Germany, the UK, Japan, etc.). As shown in *Figure 2D*, the United States has the highest number of citations of published papers (up to 34,556), followed by China [7,584].

Next, we employed CiteSpace software to draw the map of counties/regions with the strongest citation bursts (*Figure 2E*). Each bar represents a year; the red part represents the year that emerges, i.e., the period in which the citations of papers in that country/region changed significantly. The United States, Japan, and South Korea, which rank in the top 10 in terms of the number of published articles, all had the strongest citation bursts. The other five countries/regions, although not ranked in the top 10, showed outstanding results in their respective burst years, and are worthy of the attention of scientific researchers.

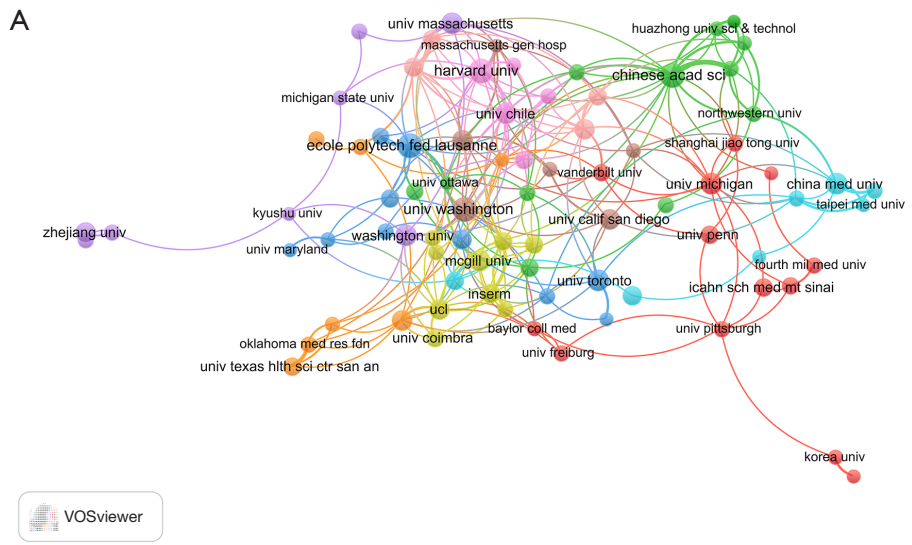
Analysis of institutions in the UPR^{mt} research area

The published papers in the UPR^{mt} research area come from 2,157 scientific research institutions, of which 83 institutions have published more than 10 papers. *Table 2* lists the top 10 institutions according to the number of published papers. Research on the UPR^{mt} was mainly conducted by universities and research institutes. Among them, Harvard University in the United States publishes the most papers (31), and the Chinese Academy of Sciences and the Swiss Institute of Technology Lausanne were tied for second (30 papers). Institutions belonging to the United States accounted for 50%, highlighting the dominant position of the United States in the field of UPR^{mt} research.

There were only two scientific research institutions belonging to China among the top 10 institutions, namely, the Chinese Academy of Sciences (30) and the China Medical University (23). The total citation frequency of papers published by Chinese institutions is relatively low, indicating that although the number of papers in this field in China is large, the quality should still be improved. As depicted in *Figure 3A*, a cooperation network of institutions in this field was established. Each node represents an institution, and each color represents a cluster, which consists of institutions that cooperate closely. In addition to the Chinese Academy of Sciences and China Medical University mentioned in *Table 2*, there are also Chinese

Table 2 The top 10 institutions according to the number of published papers [1994–2021]

Rank	Research institute	Publications (n)	Country	Citations	Co-occurrence frequency
1	Harvard University	31	USA	4,326	50
2	Chinese Academy of Sciences	30	China	943	57
3	Ecole Polytechnique Federale de Lausanne	30	Switzerland	4,741	37
4	University of Washington	29	USA	1,068	28
5	University of Chile	23	Chile	2,357	52
6	China Medical University	23	China	588	30
7	McGill University	23	Canada	1,532	22
8	University of Michigan	22	USA	3,279	23
9	University of Massachusetts	22	USA	1,684	20
10	Washington University in St. Louis	22	USA	1,232	17
11	University of Toronto	22	Canada	819	24



B

Top 8 institutions with the strongest citation bursts

Institutions	Year	Strength	Begin	End	1994–2021
Harvard Univ	1994	9.2767	2008	2015	
Univ So Calif	1994	5.0737	2008	2015	
Mem Sloan Kettering Canc Ctr	1994	5.7429	2010	2016	
Univ Munich	1994	3.9881	2011	2014	
Univ Texas Hlth Sci Ctr San Antonio	1994	3.7878	2011	2016	
Ecole Polytech Fed Lausanne	1994	6.3243	2013	2017	
Weill Cornell Med Coll	1994	4.4251	2015	2017	
Icahn Sch Med Mt Sinai	1994	4.5593	2015	2017	

Figure 3 Analysis of institutions in the UPR^{mt} research area. (A) The cooperation network of institutions in the field of UPR^{mt} research [1994–2021]. (B) The top eight institutions with the strongest citation bursts [1994–2021], the red part represents the year that emerges, the period in which the institutions with the strongest citation bursts in that institutions (each bar represents a single year). UPR^{mt}, mitochondrial unfolded protein response.

Table 3 The top 10 authors according to the number of publications [1994–2021]

Rank	Author	Records (n)	Affiliation	Country	Citations
1	Auwerx, Johan	28	Ecole Polytechnique Federale de Lausanne	Switzerland	4,621
2	Haynes, Cole m	26	University of Massachusetts	USA	3,659
3	Hetz, Claudio	13	Universidad de Chile	Chile	1,306
4	Pellegrino, Mark W	12	Memorial Sloan-Kettering Cancer Center	USA	1,383
5	Germain, Doris	12	Icahn School of Medicine at Mount Sinai	USA	429
6	Kroemer, Guido	11	University of Paris	France	3,113
7	Hood, David A	10	University of York	Canada	283
8	Shong, Minho	9	Chungnam National University	South Korea	211
9	Dillin, Andrew	9	University of California, Berkeley	USA	578
10	Samali, Afshin	9	National University of Ireland	Ireland	787

scientific research institutions such as Zhejiang University, Shanghai Jiaotong University, and the 4th Military Medical University. These universities belong to different clusters and cooperation needs to be strengthened. *Figure 3B* shows the top eight institutions with the strongest citation bursts in the field of UPR^{mt} research, but no Chinese institutions are on the list.

Analysis of authors in the UPR^{mt} research area

During the period from 1994 to 2021, there are 69 authors who published more than five papers on UPR^{mt}. The top 10 authors are listed in *Table 3*. Among them, Johan Auwerx (published 28 papers) and CM Haynes (published 26 papers) ranked in the top two in terms of the number of published papers, respectively, from the Ecole Polytechnique Federale de Lausanne and the University of Massachusetts. Also, there are four Americans in the top 10 authors, reflecting the influence of the United States in this field. However, Chinese scholars are not included in *Table 3*, indicating that the activity of Chinese researchers in this field still needs to be improved. As depicted in the cooperation network of authors, authors with the most published papers collaborate most closely with others, especially Johan Auwerx and CM Haynes (*Figure 4A*). We also focused on the citations of papers published by authors. As shown in *Figure 4B*, CM Haynes has the highest citations in published papers [1,414], followed by Johan Auwerx [799]. *Figure 4C* shows the top five authors with the strongest citation bursts that time aggregated 2011 to 2017.

Analysis of journals and research areas in the UPR^{mt} research area

We also obtained the source journals and research areas of the relevant papers from the WOS website and selected the top 10 journals and research areas, as shown in *Tables 4,5*. The *PLoS One* [50] journal has the most papers, with an impact factor of 3.788 in the past 5 years. As shown in *Table 4*, the *Cell Death and Differentiation* journal has the highest impact factor (12.774), and its Journal Citation Reports (JCR) division is Q1 in the two disciplines of biochemistry/molecular biology and cell biology, which is consistent with the research areas in *Table 5*. As depicted in *Table 4*, there are a total of six journals in the JCR division of biochemistry/molecular biology, all of which are in the Q1/Q2 division, and their impact factors are all above 5, indicating that the UPR^{mt} is relatively popular in this discipline, and thereby attract more submissions from all over the world.

Analysis of keywords in the UPR^{mt} research area

Using CiteSpace software, we established the keyword co-occurrence network in the field of UPR^{mt} research. We selected 1994–2021 for the time slicing (1 year per slice), keywords for the node type, g-index k=5, and "Pathfinder", "Pruning sliced networks", and "Pruning the merged network" for the critical path method "Pruning". *Figure 5A* depicts the co-occurrence network of keywords in the field of UPR^{mt} research. If the same keyword appears in two papers, the co-occurrence frequency of the keyword is

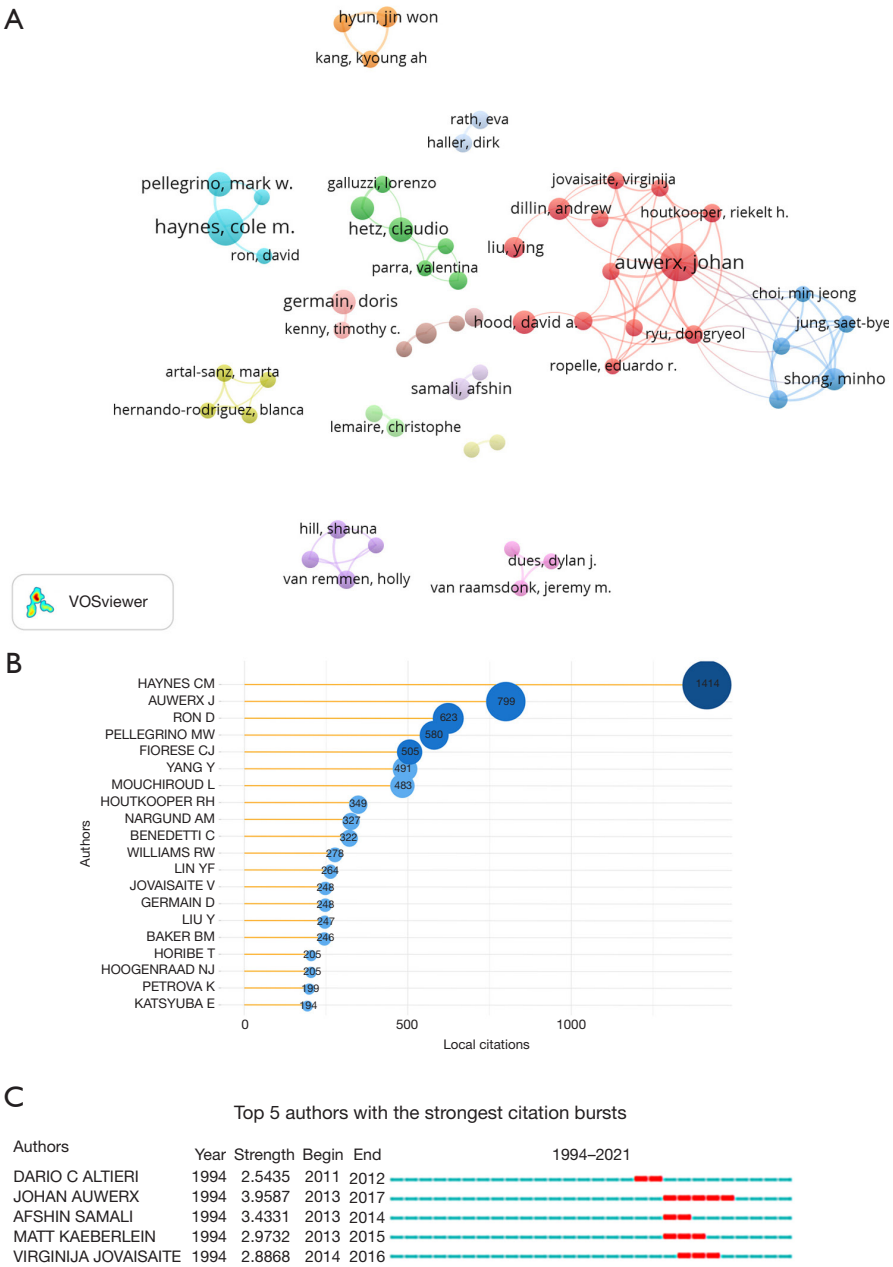


Figure 4 Analysis of authors in the field of UPR^{mt} research. (A) The cooperation network of authors in the UPR^{mt} research area [1994–2021]. (B) The top 20 authors with the highest citations of published papers [2006–2021]. (C) The top five authors with the strongest citation bursts [1994–2021], the red part represents the year that emerges, the period whoes authors with the strongest citation bursts (each bar represents a single year). UPR^{mt}, mitochondrial unfolded protein response.

1; the more times the keyword appears in different papers, the greater the co-occurrence frequency, and the larger the diameter of the circular node representing this time. The closer the connection between nodes is to yellow, the later the co-occurrence time of these two keywords in the paper; whereas, the closer the connection between nodes is to purple, the earlier the co-occurrence time of these two keywords. Moreover, unfolded protein response has the highest co-occurrence frequency in the field of UPR^{mt} research, followed by endoplasmic reticulum (ER) stress

Table 4 The top 10 journals by number of published papers [1994–2021]

Rank	Journal	Records (n)	Impact factor (past 5 years)	Research areas and JCR division (past 5 years)
1	*PLOS One*	50	3.788	Multidisciplinary science-Q2
2	*Cell Death & Disease*	40	8.713	Cell Biology-Q1
3	*Journal of Biological Chemistry*	36	5.041	Biochemistry & Molecular Biology-Q2
4	*International Journal of Molecular Sciences*	35	6.132	Biochemistry & Molecular Biology-Q1 Chemistry, Multidisciplinary-Q2
5	*Free Radical Biology and Medicine*	34	7.934	Biochemistry & Molecular Biology-Q1 Endocrinology & Metabolism-Q1
6	*Scientific Reports*	33	5.134	Multidisciplinary science-Q1
7	*Cell Death and Differentiation*	23	12.774	Biochemistry & Molecular Biology-Q1 Cell Biology-Q1
8	*Biochimica ET Biophysical ACTA-Molecular Basis of Disease*	21	6.244	Biochemistry & Molecular Biology-Q2 Biophysics-Q1
9	*Cells*	21	6.663	Cell Biology-Q2
10	*Antioxidants & Redox Signaling*	19	8.883	Biochemistry & Molecular Biology-Q1 Endocrinology & Metabolism-Q1

JCR, Journal Citation Reports.

Table 5 The top 10 well-represented research areas

Rank	Research areas	Records (n)	Proportion (%)
1	Biochemistry molecular biology	595	28.70
2	Cell biology	580	27.98
3	Neurosciences neurology	201	9.70
4	Pharmacology pharmacy	176	8.49
5	Science technology other topics	154	7.43
6	Oncology	147	7.09
7	Endocrinology metabolism	140	6.75
8	Research experimental medicine	112	6.78
9	Physiology	88	6.51
10	Biophysics	82	5.93

(*Figure 5A*). As depicted in *Figure 5B*, the cumulative co-occurrence frequency of keywords almost peaks in 2020.

Based on the keyword co-occurrence network, we selected "Find clusters-label clusters with indexing terms" to construct a clustering network. Clusters represent different research directions in the UPR^{mt} field. The keywords with the highest frequency according to the K algorithm in each cluster became the cluster tags. After screening, 13 (#0-#12) clusters were finally obtained, as depicted in *Figure 5C*. The smaller the cluster label, the more keywords the cluster contains, highlighting that the cluster is more popular. The clusters were categorized as #0 the mitochondrial unfolded protein response, #1 transcription, #2 ER stress, #3 lipotoxicity, #4 mitophagy, #5 inflammation, #6 skeletal muscle, #7 hypoxia, #8 apoptosis, #9 mitochondrial dysfunction, #10 neurodegeneration, #11

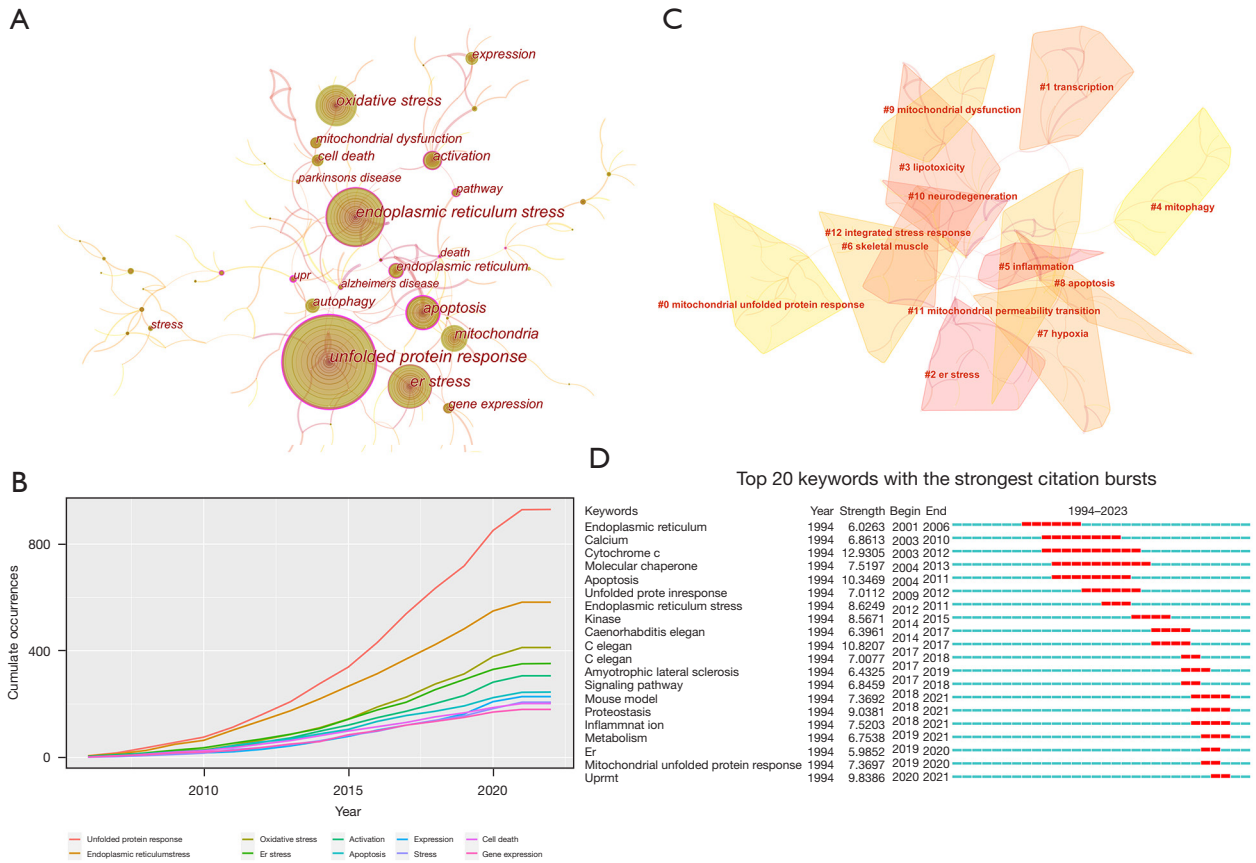


Figure 5 Analysis of keywords in the field of UPR^{mt} research. (A) The co-occurrence network of keywords in the field of UPR^{mt} research [1994–2021]. (B) The cumulative co-occurrence frequency of keywords [2006–2021]. (C) The clustering network of keywords based on the co-occurrence network. (D) The top 20 keywords with the strongest citation bursts sorted by the start year [1994–2021], the red part represents the year that emerges, the period keywords with the strongest citation bursts (each bar represents a single year). UPR^{mt}, mitochondrial unfolded protein response.

mitochondrial permeability transition, and #12 integrated stress response. *Figure 5D* shows the top 20 keywords with the strongest citation bursts. The two periods (calculated by the starting year) with relatively concentrated emergence were 2003–2004 and 2017–2019, respectively, representing that there were relatively concentrated research hotspots in the UPR^{mt} field in these two time periods. Among them, the keywords that started to emerge from 2003 to 2004 had a longer emergence time, and their emergent intensity was generally greater than that of another time period.

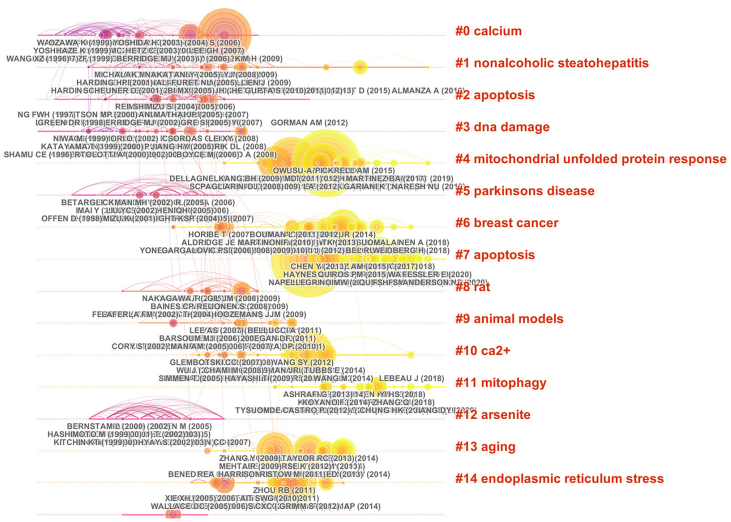
Co-citation analysis of published papers in the field of UPR^{mt} research

Figure 6A shows the timeline of co-citations of papers in the field of UPR^{mt} research. Each horizontal axis represents the development trend of a cluster; the smaller the cluster label, the more citations in the cluster. By comparing the timeline, there were obvious centralized co-citations in most clusters from 2007 to 2013, consistent with the publication years of the most highly co-cited papers listed in *Table 6*. Moreover, most of the highly co-cited papers also appear in the top 20 references with the strongest citation bursts (*Figure 6B*).

Discussion

Based on the retrieved information of published papers from the Core collection of the WOS database between 1900 and 2021, our study applied bibliometric analysis and visualization software to present the features of knowledge distribution of the field of UPR^{mt} research from both the macro and micro perspectives. Moreover, we also probed

A



B

References	Year	Strength	Begin	End	1994–2021
RON D, 2007, NAT REV MOL CELL BIO, V8, P519, DOI	2007	46.8726	2009	2015	
FIORESE CJ, 2016, CURR BIOL, V26, P2037, DOI	2016	37.579	2018	2021	
QUIROS PM, 2017, J CELL BIOL, V216, P2027, DOI	2017	29.6447	2018	2021	
NARGUND AM, 2012, SCIENCE, V337, P587, DOI	2012	28.8871	2017	2021	
DURIEUX J, 2011, CELL, V144, P79, DOI	2011	28.6469	2014	2019	
WALTER P, 2011, SCIENCE, V334, P1081, DOI	2011	27.8803	2013	2019	
SCHRODER M, 2005, ANNU REV BIOCHEM, V74, P739, DOI	2005	26.2852	2006	2013	
MELBER A, 2018, CELL RES, V28, P281, DOI	2018	26.0254	2019	2021	
SHPILKA T, 2018, NAT REV MOL CELL BIO, V19, P109, DOI	2018	25.4172	2018	2021	
HAYNES CM, 2010, J CELL SCI, V123, P3849, DOI	2010	24.3545	2012	2017	
NARGUND AM, 2015, MOL CELL, V58, P123, DOI	2015	24.0877	2016	2021	
SZEGEZDI E, 2006, EMBO REP, V7, P880, DOI	2006	22.7826	2008	2014	
NAKAGAWA T, 2000, NATURE, V403, P98, DOI	2000	22.7767	2003	2008	
OYADOMARI S, 2004, CELL DEATH DIFFER, V11, P381, DOI	2004	22.6326	2008	2012	
HETZ C, 2012, NAT REV MOL CELL BI0, V13, P89, DOI	2012	21.2766	2015	2019	
HAYNES CM,2010, MOL CELL,V37, P529, DOI	2010	20.4334	2013	2018	
HAYNES CM,2007, DEV CELL,V13, P467, DOI	2007	18.8937	2009	2015	
PUTHALAKATH H, 2007, CELL, V129, P1337, DOI	2007	17.9346	2008	2014	
TIAN Y, 2016, CELL, V165, P1197, DOI	2016	17.774	2017	2021	
XU CY, 2005, J CLIN INVEST, V115, P2656, DOI	2005	17.7624	2009	2013	

Figure 6 Co-citation analysis of published papers in the field of UPR^{mt} research. (A) Timeline of co-citations of papers in the UPR^{mt} field [1994–2021]. (B) The top 20 references with the strongest citation bursts [1994–2021], the red part represents the year that emerges, the period in which references with the strongest citation bursts (each bar represents a single year). UPR^{mt}, mitochondrial unfolded protein response.

the intellectual bases and research hotspots in this field.

The UPR^{mt} research has gone through the infancy and rapid growth phases in terms of the number of published papers. After 2000, the number of papers on the UPR^{mt} began to increase, and achieved rapid growth especially after 2010. In terms of the macro-geographical distribution, the United States and China have contributed the most to UPR^{mt} research. The global geographic distribution demonstrates that North America, East Asia, and Europe are hotspots for UPR^{mt} research, highlighting the need for most South American and African countries to increase their outputs. Although China ranks second in terms of the total number of published papers, the total citation frequency is not high, meaning that Chinese research in this field needs to be more comprehensive. As for the distribution of institutions, Harvard University is the most influential institution in the field of UPR^{mt} research.

From the microscopic knowledge distribution characteristics, the most prolific authors are Johan Auwerx and CM Haynes. Despite the number of articles published by core authors was not large, but their theory or research has a significant impact on the development of UPR^{mt}. *PLoS One* is the most extensive journal in the study of UPR^{mt}, while the *Cell Death and Differentiation* journal has the highest impact factor among the most-authored journals. Moreover, biochemistry/molecular biology and cell biology are the largest subject areas in the field of UPR^{mt} research.

This study also revealed the knowledge base and research hotspots in UPR^{mt} research through co-citation analysis as well as high-frequency keyword clustering

Table 6 The top 10 most cited papers [1994–2021]

Rank	Title	Publication year	First author	Co-citations (n)
1	Signal integration in the endoplasmic reticulum unfolded protein response	2007	Ron, David	272
2	A mitochondrial specific stress response in mammalian cells	2002	Zhao, Q	248
3	Mitochondrial import efficiency of ATFS-1 regulates mitochondrial UPR activation	2012	Nargund, AM	241
4	The unfolded protein response: from stress pathway to homeostatic regulation	2011	Walter, P	204
5	ClpP mediates activation of a mitochondrial unfolded protein response in C-elegans	2007	Haynes, CM	197
6	Mitonuclear protein imbalance as a conserved longevity mechanism	2013	Houtkooper, RH	191
7	The cell-non-autonomous nature of electron transport chain-mediated longevity	2011	Durieux, J	190
8	Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones	2004	Yoneda, T	175
9	The matrix peptide exporter HAF-1 signals a mitochondrial UPR by activating the transcription factor ZC376.7 in C-elegans	2010	Haynes, CM	164
10	The mammalian unfolded protein response	2005	Schroder, M	160

analysis. UPR^{mt} research is divided into the following 13 parts: #0 mitochondrial unfolded protein response, #1 transcription, #2 ER stress, #3 lipotoxicity, #4 mitophagy, #5 inflammation, #6 skeletal muscle, #7 hypoxia, #8 apoptosis, #9 mitochondrial dysfunction, #10 neurodegeneration, #11 mitochondrial permeability transition, and #12 integrated stress response. These 13 components form the knowledge base of UPR^{mt} research.

Multi-country collaborations often create channels to facilitate the dissemination of knowledge and access to funding for organizations that may not be able to afford high-end technologies (32-34). Thus, increased knowledge dissemination enhances the research quality in the field of UPR^{mt} research. Nevertheless, this study has some limitations that should be noted. Firstly, although bibliometric analysis is capable of bringing about a few intriguing clustering outcomes, it is unfortunately still not as in-depth as traditional literature reviews. Therefore, our understanding of this particular scientific field should be supplemented based on the bibliometric analysis. Secondly, when selecting the original data, this paper only analyzed papers in the Core Collection of the WOS database, and the analysis results may have certain deviations. For further in-depth research in this field in the future, it is necessary to refer to other databases for a more comprehensive analysis and summary.

Conclusions

In this study, based on the Core Collection of the WOS database, a bibliometric and visual analysis of the UPR^{mt} field was carried out using CiteSpace and VOSviewer software. We objectively depicted the scientific research cooperation network, development trend, and research direction in this field, which has a certain referential significance for subsequent research.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6423/coif).

The authors have no conflicts of interest to declare.

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