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Mitochondrial Dysfunction: A Bibliometric Analysis from 2002 To 2022

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Abstract: Studying mitochondrial dysfunction can understand the principle of mitochondrial dysfunction, so as to better treat diseases caused by mitochondrial dysfunction. A growing body of research suggests that diseases produced by mitochondrial dysfunction can be treated with medications. However, to date, there has been no bibliometric study in this area. Our study aimed to visualize the publications to determine the hotspots and frontiers in research on mitochondrial dysfunction and provide direction for further research. The search strategy set in the database with "Mitochondrial dysfunction*", and 8130 articles were obtained after being automatically filtered by Citespace 4604 articles. We used CiteSpace6.1, R1, VOSviewer 1.6.18 and Excel 2019 software tools to conduct this bibliometric study. The study of mitochondrial dysfunction has now tended to be perfect. But in the future, the links between countries, institutions, and in particular, authors should be strengthened. At present, the research on mitochondrial ROS content imbalance and mitochondrial oxidative stress has gradually decreased, and the research on mitochondrial autophagy and mitochondrial kinetic disorders has increased and has become an emerging hot spot.

1. Introduction

Mitochondria were bilayer membrane organelles present in most cells that provide ATP to cells. And it can maintain the cell's Ca^{2+} balance and ROS balance, known as the "power house". At the same time, the mitochondria contain DNA, but due to their small DNA content, they cannot fully control their own life activities, which are also called semi-autonomous organelles. In addition, mitochondria are involved in processes such as apoptosis of cells (by inducing the release of apoptotic factors or regulating membrane potentials), differentiation, and information transmission. In addition, mitochondria can also regulate cell proliferation and control cellular metabolism (for example, by influencing the metabolism of macrophages to prevent wound healing, which has a lot to do with the complications of type 2 diabetes that are not cured). In special organs such as the liver, mitochondria also exhibit detoxifying functions. So, it plays a vital role in the organism.

Mitochondrial dysfunction has been found to cause a variety of diseases. Including neurodegenerative diseases such as Alzheimer's disease and Parkinson's diseases [1], and cancer (breast, prostate, and colon cancers) [2]. It can also cause a variety of diseases such as diabetic kidney disease [3], diabetic retinopathy [4], cardiovascular diseases, Metabolic inflammation, Chronic liver disease, Chronic kidney disease, Pulmonary fibrosis, bipolar disorder and other diseases. Most of the causes of these diseases were mitochondrial mtDNA (mitochondrial DNA) and DNA mutations,

which make it impossible to express them in a coordinated manner [1-3], resulting in increased ROS content and destroying the internal structure of the mitochondria and their stability [5]. Mitochondrial dysfunction can be assessed using isolated mitochondria, and mitochondria proton current (respiration rate) was measured to determine mitochondrial function. Mitochondrial dysfunction was closely related to a variety of diseases, so a large number of targeted drugs have emerged, and the study of mitochondrial dysfunction has become a research hotspot for 20 years.

2. Material and methods

2.1 Data sources and search policies

The data used in this study were from the Web of Science Core Collection (WOSCC), the world's most important database for academic information. The search formula used is TS = "Mitochondrial dysfunction *", limiting the publication year of the article from 2002 to 2022, without limiting the article type and language.

2.2 Data collection and analysis

The searched data records full records and references were output in plain text format. The literature search and data download were completed on May 1, 2022. A total of 8130 articles were retrieved in Citespace to find 7360 articles, finally screened by Citespace, a total of 4604 articles were determined to be used for visual analysis after the final screening. Figure 1 showed the flowchart of document selection.

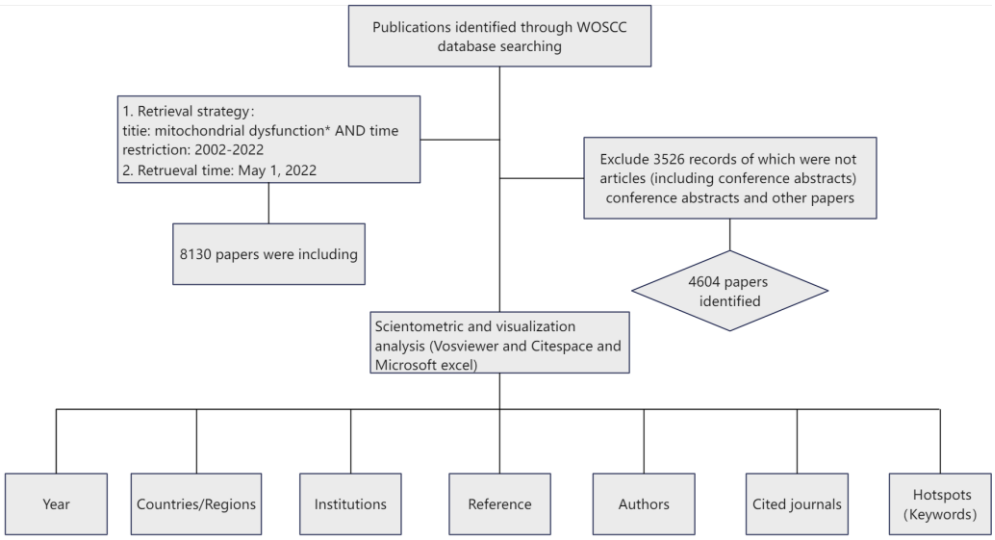

Figure 1: Literature anthology flowchart of this article which is about mitochondrial dysfunction.

2.3 Literature Visual Analysis

VOSviewer v1.6. 18 Scientific knowledge graphs can be mapped through web data (all from the Web of Science) for the generation of visual maps, co-author analysis, analysis of countries and institutions, co-cited authors and co-cited references, keyword clustering, and more. The keyword co-occurrence network visualization was a way to identify research hotspots and predict research trends [6]. CiteSpace v6.1. R1 parameters: time span (2002-2022), year per slice (1). Analyze the explosive words, the presence of explosive words can explain the research direction and development trend of mitochondrial dysfunction. Microsoft Office Excel 2019 was used to output data tables, draw

histograms, organize, summarize and more.

3. Results

3.1 Annual Growth Trend of Publications

We identified a total of 4604 studies, published between 2002 and 2022. We show the change in the number of annual publications over the last 20 years in the form of a histogram (see Figure 2), reflecting trends in the field. From 2002 to 2022, the number of publications on mitochondrial dysfunction generally showed a year-on-year trend (except for a transient downward trend in 2009), and the cumulative number continued to increase. Between 2002 and 2007, the number of publications was < 100, between 2008 and 2015, the number of publications was between 100-200, and between 2012-2019. The number of publications between the years was between 200-400 and the number of publications in 2020-2021 was >500.

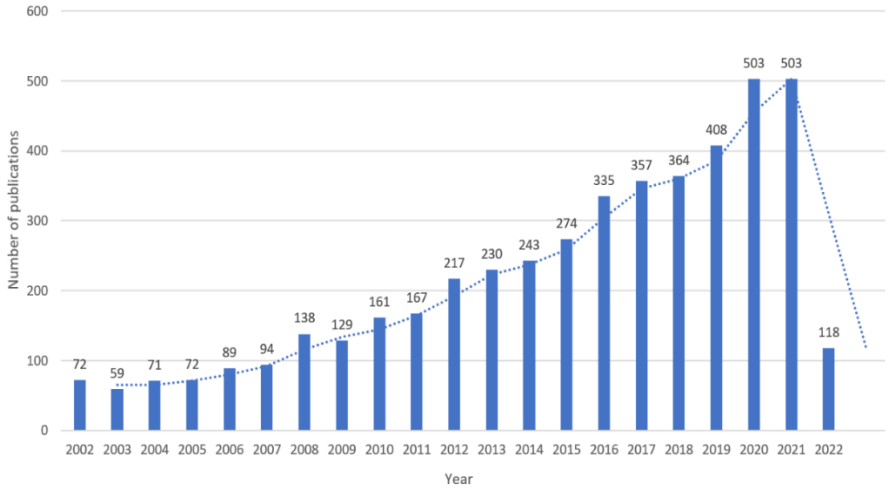

Figure 2: Histogram of annual publications related to mitochondrial dysfunction research, 2002-2022.

3.2 Countries/Regions and Institutions Analysis

Between 2002 and 2022, a total of 85 countries contributed to publications related to mitochondrial dysfunction. Table 1 shows the top 10 most productive countries, and the table shows that the United States was the country with the largest number of articles published, with a total of 1391 articles, followed by China, with a total of 1299 articles. Other countries have published less than 300 articles. As shown in Figure 3 (A), the countries/regions (45/85, 52.94%) with the publication number greater than or equal to 10 (T = 10) were used to construct the co-authorship network. In this network map, the United States (764/1802, 42.40%) and China (317/1802, 17.59%) have larger sizes of nodes, representing more publications. And mainly these two countries constitute a cooperative network. It was worth noting that although some countries do not publish much literature, they have strong cooperation with other countries, such as the United Kingdom and Germany. Since the darker, the node colour means that the earlier the publication year, it can be judged that the United States, Japan, France, Italy, Germany, Spain, and other countries studied "mitochondrial dysfunction" earlier, and China studied the field later, but the number of published documents has reached the second. According to Figure 3 (B), it can be judged that these cooperating countries were mainly concentrated in Asia, North America, and Europe.

Table 1: Top 10 countries/regions and institutions of mitochondrial dysfunction research publications.

Rank	country/region	count	organization	count
1	USA	1391	Shanghai Jiao Tong University (China)	55
2	China	1299	Chinese Academy of Sciences (China)	55
3	India	285	Nanjing Medical University (China)	52
4	South Korea	276	Sun Yat Sen University (China)	52
5	Japan	232	University of Pennsylvania (United States)	49
6	Italy	229	Fudan University (United States)	49
7	United Kingdom	228	Xi'an Jiao Tong University (China)	48
8	Germany	207	University of Coimbra (Portugal)	47
9	Spain	154	Harvard University (United States)	46
10	France	151	Fourth Military Medical University (China)	44

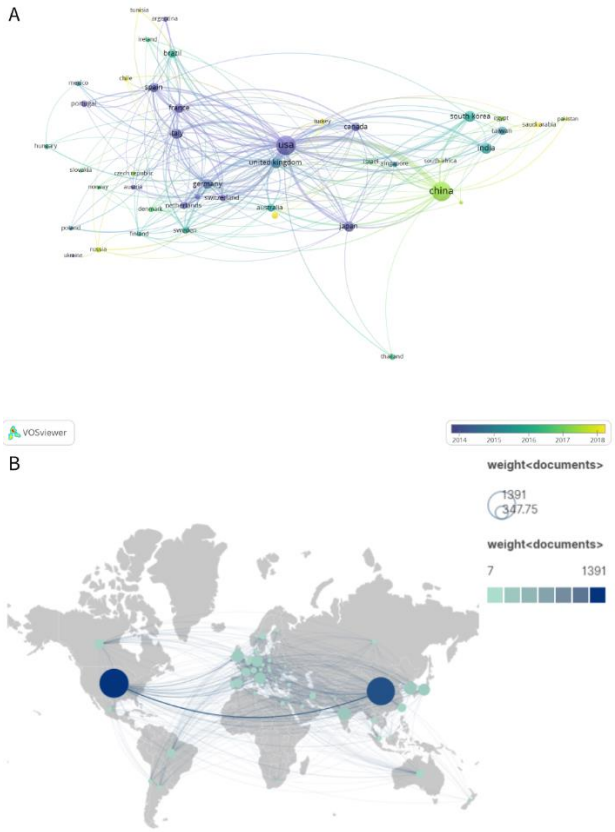

Figure 3: Cooperative networks between countries. Node sizes represent the number of releases, connection sizes were cooperative intensity, early contributions were darker. (B) Import country/region data into Scimago Graghica. The node size was the number of documents, the more documents the larger the node. The node colour was the number of documents, and the more documents the darker the colour. The thickness of the connection was the strength of the connection, and the thinner the line, the smaller the strength of the connection.

The top 10 institutions were distributed in five countries/regions, three-fifths of which were located in China. A total of six institutions published more than 300 papers: Shanghai Jiao Tong University, Chinese Academy of Sciences, Nanjing Medical University, Sun Yat Sen University, Xi'an Jiao Tong University and Fourth Military Medical University. The institutional cooperation network shown in Figure 4 involves 158 agencies and 8366 links. Among the many institutions at home and abroad, a cooperation network centered on Harvard University (46 articles) (total cooperation intensity of 224), Nanjing University (52 articles), and the University of Pennsylvania (49 articles) have been formed, but we found that the institutions with the largest number of articles published were Shanghai Jiao Tong University (55 articles) and the Chinese Academy of Sciences (55 articles), but the cooperation intensity of the two institutions was weaker than that of the above institutions (the total cooperation intensity was less than 150).

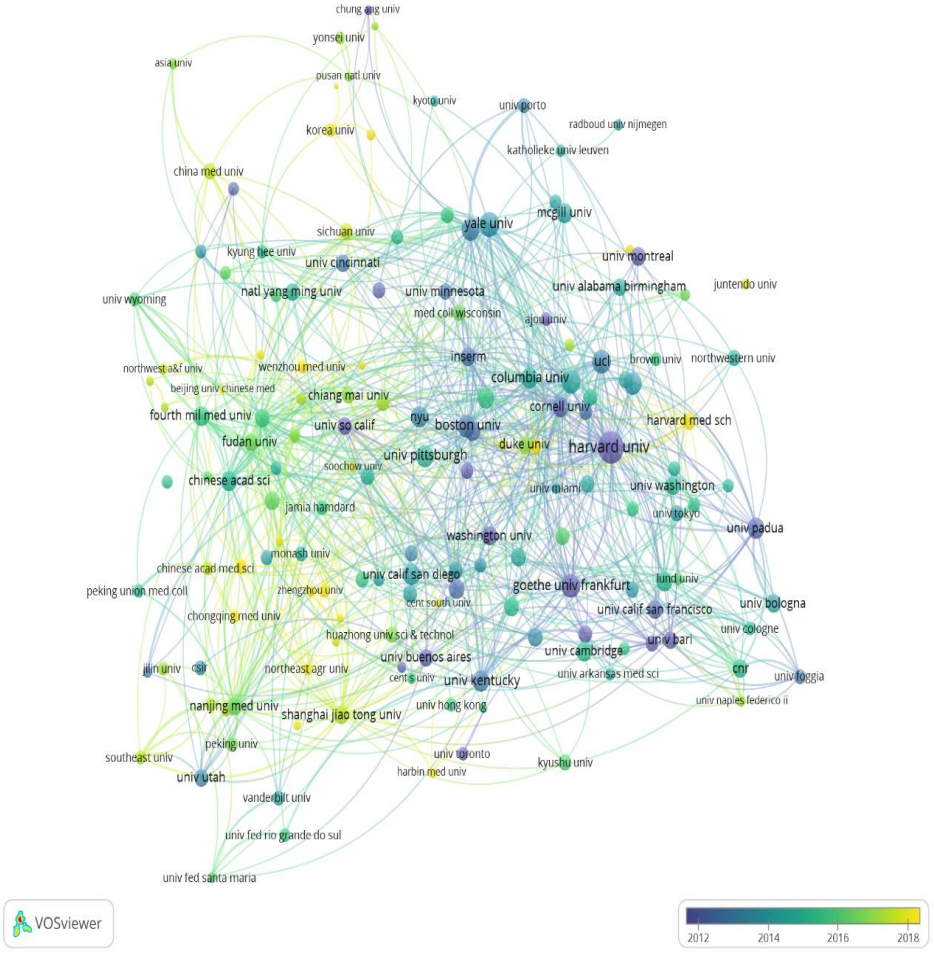

Figure 4: The network of institutions engaged in the research about mitochondrial dysfunction. Node size indicates the number of releases, the connection size was the strength of the collaboration, and the early contribution colour was darker.

3.3 Journals and Co-Cited Academic Journals

A total of 3210 publications, related to mitochondrial dysfunction, were published in 1075 academic journals. Among the many magazines, most of them were from the United States, and in the top 10 magazines, except *Free Radical Biology & Medicine* (Netherlands), *Scientific Reports* (United Kingdom), and except for *Mitochondrion* (Netherlands), and *Neurochemistry International* (United Kingdom), the rest were from the United States (see Table 2). *Plos One* (United States)

published the most papers (n=124), followed by *Free Radical Biology & Medicine* (Netherlands, n=88), *Scientific Reports* (United Kingdom, n=87), and *Journal of Biological Chemistry* (the United States, n=70). Among 9948 co-cited academic journals, most of them were from the United States, except for the *Free Radical Biology & Medicine* (Netherlands), *Nature* (United Kingdom), and *Journal of Neurochemistry* (United Kingdom) (see Table 3). *Journal of Biological Chemistry* (United States) had the most co-citations (n = 8469), followed by *Proceedings of the National Academy of Sciences of the United States of America* (the United States, n=5205), *Free Radical Biology & Medicine* (the Netherlands, n=3608) and *Nature* (the United Kingdom, n=3608).

Table 2: Cited journal analysis on mitochondrial dysfunction.

	co-cited journal	citations	journal	documents
1	***Journal of Biological Chemistry* (United States)**	**8469**	***Plos One* (United States)**	**124**
2	***Proceedings of the National Academy of Sciences of the United States of America* (United States)**	**5205**	***Free Radical Biology & Medicine* (Netherlands)**	**88**
3	***Free Radical Biology & Medicine* (Netherlands)**	**3608**	***Scientific Reports* (United Kingdom)**	**87**
4	***Nature* (United Kingdom)**	**3439**	***Journal of Biological Chemistry* (United States)**	**70**
5	***Science* (United States)**	**3162**	***Mitochondrion* (Netherlands)**	**69**
6	***Plos One* (United States)**	**3146**	***Biochemical and Biophysical Research Communications* (United States)**	**66**
7	***Cell* (United States)**	**2743**	***International Journal of Molecular Sciences* (United States)**	**66**
8	***Journal of Neurochemistry* (United Kingdom)**	**2543**	***Oxidative Medicine and Cellular Longevity* (United States)**	**61**
9	***Journal of Neurology and Experimental Neuroscience* (United States)**	**2434**	***Molecular Neurobiology* (United States)**	**51**
10	***Diabetes* (United States)**	**2070**	***Neurochemistry International* (United Kingdom)**	**47**

Table 3: Top 10 co-cited authors on mitochondrial dysfunction.

Rank	author	documents	total link strength
1	Chattipakorn N	35	98
2	Chattipakorn S	34	98
3	Liu JK	22	38
4	Lim HS	18	18
5	Song GH	18	18
6	Jaiwongkam T	13	52
7	Liu Y	13	3
8	Kerdphoo S	12	50
9	Li Y	12	6
10	Raza H	12	12
11	Ren J	12	6
12	Rodenburg R	12	1
13	Wang Q	12	4
14	Wang W	12	5
15	Zhang AH	12	34

3.4 Document Co-Citation Network

Document Co-Citation Network reflects the latest research trends and scientific trends. Figure 5 showed a visual image of a literature reference based on cite space. Includes 111301 references (only 1210 highly cited documents were used for graphical analysis) and 2278 co-citation connection points. It was mainly carried out in the literature as the central network shown in Figure 5. In Figure 6 we show the top 25 burst citations, which were consistent with the citations shown in Figure 5. Figure 5 was the largest node and most cited Lin m, 2006, published in nature, cited 155 times, entitled "Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative diseases" concludes that mitochondrial dysfunction accelerates aging [7]. Followed by Murphy M et al. study Mitochondrial Phenotyping on Fibroblasts [8], Brand M et al. studied the role of co-activator complexes in RNA polymerase II transcription.

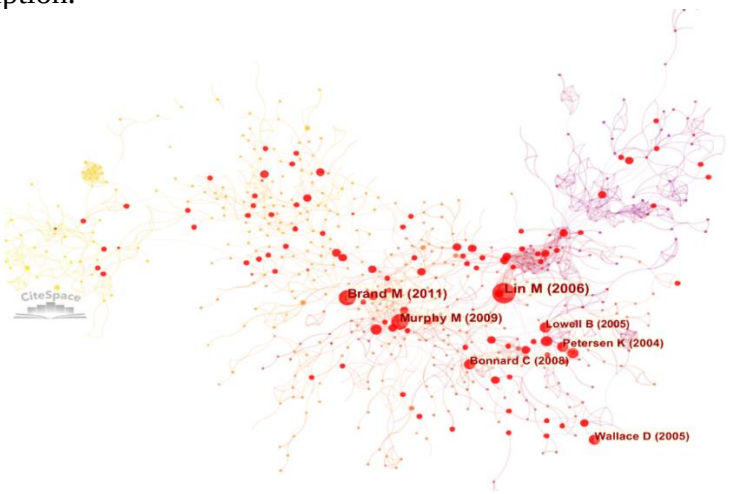

Figure 5: The document co-citation network analysis. The dark colour of the node and link was the early common reference relationship, and the light colour was the later colour. Those with > 18 citation references can display the author's name and the time of creation. The node size represents the size of the number of citations that have been cited.

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2002 - 2022
Kroemer G, 2000, NAT MED, V6, P513, DOI 10.1038/74994, DOI	2000	9.8	2002	2004	
Green D, 1998, SCIENCE, V281, P1309, DOI 10.1126/science.281.5381.1309, DOI	1998	9.21	2002	2003	
Wallace D, 1999, SCIENCE, V283, P1482, DOI 10.1126/science.283.5407.1482, DOI	1999	7.49	2002	2004	
Casley C, 2002, J NEUROCHEM, V80, P91, DOI 10.1046/j.0022-3042.2001.00681.x, DOI	2002	6.53	2003	2007	
Petersen K, 2003, SCIENCE, V300, P1140, DOI 10.1126/science.1082889, DOI	2003	8.05	2004	2008	
Lustbader J, 2004, SCIENCE, V304, P448, DOI 10.1126/science.1091230, DOI	2004	7.49	2005	2007	
Green D, 2004, SCIENCE, V305, P626, DOI 10.1126/science.1099320, DOI	2004	6.72	2005	2009	
Petersen K, 2004, NEW ENGL J MED, V350, P664, DOI 10.1056/NEJMoa031314, DOI	2004	10.78	2006	2008	
Mootha V, 2003, NAT GENET, V34, P267, DOI 10.1038/ng1180, DOI	2003	8.07	2006	2008	
Lowell B, 2005, SCIENCE, V307, P384, DOI 10.1126/science.1104343, DOI	2005	7.55	2006	2010	
Beal M, 2005, ANN NEUROL, V58, P495, DOI 10.1002/ana.20624, DOI	2005	6.28	2006	2010	
Balaban R, 2005, CELL, V120, P483, DOI 10.1016/j.cell.2005.02.001, DOI	2005	6.28	2006	2010	
Lin M, 2006, NATURE, V443, P787, DOI 10.1038/nature05292, DOI	2006	17.98	2007	2011	
Wallace D, 2005, ANNU REV GENET, V39, P359, DOI 10.1146/annurev.genet.39.110304.095751, DOI	2005	8.86	2007	2010	
Ritov V, 2005, DIABETES, V54, P8, DOI 10.2337/diabetes.54.1.8, DOI	2005	6.05	2007	2010	
Keeney P, 2006, J NEUROSCI, V26, P5256, DOI 10.1523/JNEUROSCI.0984-06.2006, DOI	2006	6.81	2008	2009	
Narendra D, 2008, J CELL BIOL, V183, P795, DOI 10.1083/jcb.200809125, DOI	2008	5.91	2009	2013	
Murphy M, 2009, BIOCHEM J, V417, P1, DOI 10.1042/BJ20081386, DOI	2009	12.26	2010	2014	
Bonnard C, 2008, J CLIN INVEST, V118, P789, DOI 10.1172/JCI32601, DOI	2008	9.23	2010	2013	
Brand M, 2011, BIOCHEM J, V435, P297, DOI 10.1042/BJ20110162, DOI	2011	15.16	2012	2016	
Du H, 2010, P NATL ACAD SCI USA, V107, P18670, DOI 10.1073/pnas.1006586107, DOI	2010	7.21	2012	2015	
Lee J, 2012, BIOCHEM J, V441, P523, DOI 10.1042/BJ20111451, DOI	2012	6.22	2013	2017	
Youle R, 2012, SCIENCE, V337, P1062, DOI 10.1126/science.1219855, DOI	2012	7.01	2014	2017	
Zorov D, 2014, PHYSIOL REV, V94, P909, DOI 10.1152/physrev.00026.2013, DOI	2014	8.92	2017	2018	
Bhat A, 2015, BIOMED PHARMACOTHER, V74, P101, DOI 10.1016/j.biopha.2015.07.025, DOI	2015	7.43	2017	2019	

Figure 6: The top 25 references with the strongest citations bursts. Each red bar refers to the burst duration, the blue bar indicates the publication time of the references and the year column was the publication time of the reference. The bursts indicate the direction and trend of the study.

3.5 Author Co-Citation Network

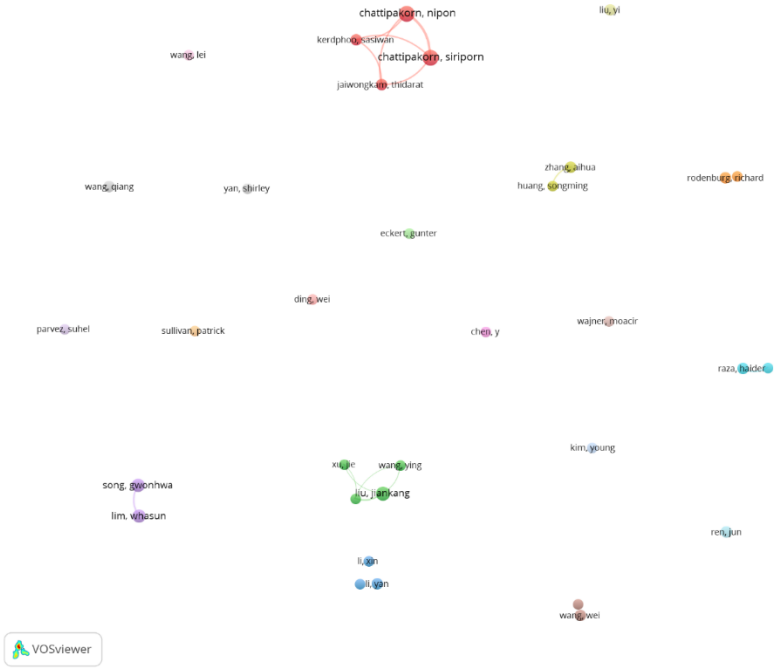

Figure 7: The network of authors contributed to mitochondrial dysfunction. In the network, the larger the node was, the more contribution the author had made to that field. The size of the node represents the amount of text, the line thickness was the contact strength, the thicker the line, the greater the contact strength. Different colours were different clusters, and the same colour was the same cluster.

The authors co-cite the network, identifying frequently cited academics who have globally recognized publications on mitochondrial dysfunction, handled by VOSviewer, shown in Figure 7, achieving a network with 33 nodes and 161 links. Among the 26564 authors， the authors (33/26564, 0.124%) with a publication number greater than or equal to 10 (T=10) were used to construct the co-authorship map. Among them, Thailand's Chattipakorn N has the largest number of publications (35 articles) and the strongest cooperation intensity (98/161, 59.63%), he and Chattipakorn S, Jaiwongkam T, Kerdphoo T, Sasiwan work closely together. There were also South Korea's Lim HS (18 articles) and Song GH, and China's Xu J, Wang J, Liu JK, Li X, and Li Y worked closely together.

3.6 Analysis of Research Hotspots

The keyword clustering analysis using VOSviewer was shown in Figure 8. The cluster network consisted of 92 nodes and 1511 links. (Only links with a minimum link strength of 7 were shown in the Figure) The different colours in the graph represent different clusters, indicating different directions. The number of keywords contained in each cluster was as follows: Cluster 1 (red): 17 items; Cluster 2 (green): 16 items; Cluster 3, Cluster 4:15 items; Cluster 5 (pink): 12 items; Cluster 6 (light blue): 10 items; Cluster 7 (orange): 7 items. The largest cluster was cluster 1, shown in red in Figure 8, and the cluster was more dispersed by acute kidney injury, atp, complex i, and so on electron transport cha, glutathione, hypoxia, schemia, membrane potential, mitochondrial mitochongron, Neurodegeneration, nitric, oxide, oxidative phosphoryla, Parkinson’s disease, proteomics, respiration, rotenone Composition, research direction was reflectory chain. Followed by cluster 2, which was green, consisting of ampk, bioenergetics, diabetes, diabetic cardiomyopa, exercise, heart, insulin resistance, metabolic syndrome, mitochondrial biogen, mitochondrial function, obesity, pgc-1 alpha, resveratrol sirt1, skeletal muscle, type 2 diabetes, research directions were insulin resistance and metabolic syndrome. In the remaining clusters Cluster 7 (orange) studies oxidative stress, Cluster 3 (blue) studies apoptosis, and Cluster 5 (pink) studies disease classes.

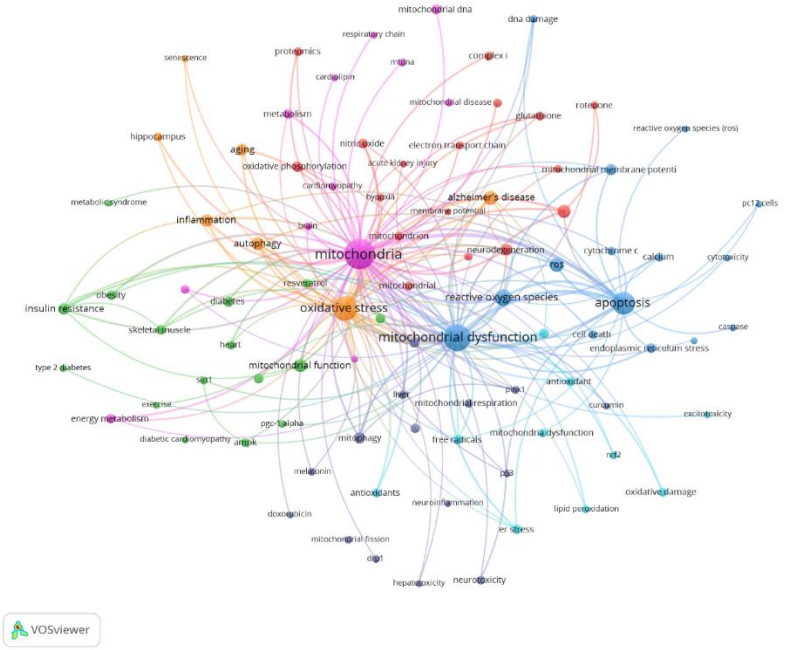

Figure 8: The network visualization of keywords. Based on the keyword clustering analysis graph made by VOSviewer, there were 7 clusters in the graph. The labels before clustering were sorted by the size of the cluster. From 1-7, the cluster intensity gradually weakens, of which 1 cluster strength was the largest and contains the most literature.

Figure 9 was based on the first 25 explosive words made by Citespace, sorted by year of appearance, of which the shortest duration was 2 years (stem cell), The strength of the keywords was 7.18-29.24, and the duration of the bursts was 2-12 years. After 2019, mitophagy, dynamics, autophagy, and ampk were often cited.

Figure 9: Top 25 keywords with the strongest citation bursts. Each red bar refers to the burst duration, the blue bar indicates the publication time of the keywords and the year column was the burst time of the strongest citation. The bursts indicate the direction and trend of the study.

4. Discussion

4.1 General Information

Overall, the large number of publications in 2002-2022 indicates that this period was rich in research, with deep research on the area of mitochondrial dysfunction, which was not an emerging area. Figure 1shows that 72 articles have been published in 2002, suggesting that researchers had studied the area of mitochondrial dysfunction before 2002. Since 2016, there has been an explosive increase in publications on mitochondrial dysfunction to more than 300, and the research field has gradually expanded.

The cooperation network analysis of authors can provide information on influential research groups and potential collaborators and was helpful to establish collaborations for researchers [9]. As

shown in Figure 7, although many authors have studied this field, the strength of the association between the authors was not high, and even there was no connection between many authors who have published a large number of documents. Among the top ten authors, Chattipakorn, Nipon Chattipakorn, and Siriporn were the authors of >30 articles, and the centrality of these two authors exceeds 0.1, indicating that they were leaders in research in this field, and the articles were representative and authoritative. Seven of the top ten authors were from China, and six of the top ten institutions were from China (see Table 1), but China's centrality was not as high as that of the United States (American centrality was 0.46), and the top 10. The number of published journals was dominated by the United States, indicating that the United States has a high influence in this regard. Therefore, it was strongly recommended that China should strengthen cooperation with the United States and other countries to jointly study mitochondrial dysfunction and promote the development of this field.

The first 5 commonly cited references mainly include the following aspects: (1) The relationship between mitochondrial dysfunction and inherited neurodegenerative disease; (2) Mitochondrial fusion and escaped cause mitochondrial dysfunction, which causes the cellular function to decline [10]; (3) Kinase1 (PINK1) mutations or mitochondrial telomeres (telomerase RNA) mutations cause mitochondrial dysfunction [11-13]; (4) An age-associated decline in mitochondrial function contributes to insulin resistance in the elderly [14]. These literatures have an earlier publication date and a more comprehensive analysis, laying a foundation for the study of mitochondrial dysfunction. Researchers have begun to cover a wide range of diseases, not only inherited neurodegenerative disease, but also about diabetes and the associated complications it causes. Although the research areas were broader, other areas of mitochondrial dysfunction have yet to be developed.

4.2 The Hotspots and Frontiers

Keyword analysis can help us understand the hotspots and frontiers in the field we studied. As can be seen from Figure 8, keywords that appear more frequently were active stress, mitochondrial dysfunction, apoptosis, expression, activation, mechanism, disease, cell death, inhibition, metabolism, cell, protein, alzheimers disease, Skeletal muscle, nitric oxide, etc., eventually form 7 clusters. Keywords make the literature the core content of the research topic. We learned that over the past 20 years, researchers have focused on the following three areas.

The first was to study the mechanism of mitochondrial dysfunction. Mitochondria are considered "energy metabolism factories of living organisms" and are the places where cells breathe. Its main functions are energy conversion, citric acid circulation, oxidative phosphorylation, storage of Ca^{2+} and so on. The results of our study focus on apoptosis, reactive oxygen species, oxidative stress, mitochondrial dynamic imbalance, and more. (1) Imbalance of mitochondrial oxidative stress: oxidative stress is a state in which the cellular antioxidant defense system is not enough to keep the level of reactive oxygen species (ROS) below the toxicity threshold, which is an imbalance between oxidation and antioxidant effects in the body [15]. For the body, the appropriate amount of ROS can protect the body from external substances and regulate its biological balance, but excessive ROS will cause oxidative damage to DNA, lipids, and proteins. Causes disruption of cellular structures; (2) Mitochondrial dynamics disorders: Mitochondrial dynamics mainly include splitting, fusion, and dynamic equilibrium between fusion and fission. Imbalances in mitochondrial dynamics can lead to problems with mitochondrial quality control, exposing the mitochondria to stress damage. At the same time, because the mitochondria cannot autophagy, the aging and damaged mitochondria accumulate, resulting in irreversible damage to the mitochondria. In the article by Nunnari J, Suomalainen A, the relationship between mitochondrial dynamics and autophagy and apoptosis was explained from the Roles of Mitochondrial Dynamics and autophagy and apoptosis, respectively

(Nunnari and Suomalainen, 2012); (3) In the madreiter-Sokolowski CT and others, it was found that in a patient with inflammation, the content of Ca^{2+} in the body would be significantly higher than that of normal people [16], and calcium overload would activate this dependent protease caused Increased ROS levels while stimulating miochondrial permeability transition pores, the opening of MPTP (miochondrial permeability transition pores), the release of Apoptosis factor, and cell death [16-20], and the process continues to create a vicious circle. Understanding the mechanism of mitochondrial dysfunction, it helps researchers to give reasonable drug treatment methods for different stages.

The second was the study of various diseases caused by mitochondrial dysfunction. Over the past 20 years, researchers have explored some of the diseases that mitochondria cause, involving neurodegenerative diseases (NDDs) such as Alzheimer diseases and Parkinson's diseases, cancer (breast, prostate, and colon cancers) as well as kidney damage, diabetes and its complications and other diseases. (1) A large body of research literature suggests that changes in the parkin-Pink1 pathway or biogenesis of mitochondria affect Mitophagy, making it impossible for damaged cells to clear, thus exacerbating it Occurrence of neurodegenerative diseases [11, 21-29]. (2) And for cancer, Increasing ROS levels and products of the oxidative stress, mitochondrial DNA genetic mutations, ROS have regulatory roles in cell Death and proliferation, once its equilibrium was upset, will not be able to control the growth cycle of tumor cells, triggering cancer [2, 30-37]; (2) The initiation of T2DM (Type 2 diabetes mellitus) may be related to factors such as energy substrate metabolism, reactive oxygen species (ROS) generation, and apoptosis [17, 38-41]; (3) In organs like the heart, which have a high energy demand, once cardiovascular disease was produced, it affects the need for oxygen and nutrients in the mitochondria leads to a progressive decline of the mitochondrial function associated with abnormalities in the respiratory chain and ATP synthesis, oxidative stress was disrupted, exacerbating cardiovascular disease [42-44]. In academia, mitochondrial dysfunction can cause a variety of diseases that have become widely accepted and been studied in deeper areas. Other related studies have also shown that mitochondrial dysfunction is also associated with depression, ASDs (autism spectrum disorders), ipotoxicity, Metabolic inflammation, Chronic liver disease, Chronic kidney disease, Pulmonary fibrosis, bipolar disorder and other diseases are involved.

The third was the clinical treatment of diseases caused by mitochondrial dysfunction. Calcium treatment focuses on the treatment of cancer. Since mutations in mitochondrial mtDNA (mitochondrial DNA) cause mitochondrial dysfunction, Tomitita K, Kuwahara Y et al. proposed by studying cancer resistance and the mitochondrial condition Therapeutic strategy employing mitochondrial transplantation (mtTP) to treat cancer [45]. Guerra F dengren proposed the use of glycolysis, glutaminolysis, oxidative phosphorylation, and retrograde signaling to prevent chemoresistance [46]. In a clinical trial conducted by El-Hattab AW, et al., Nishi Wang treats diseases caused by mitochondrial dysfunction by enhancing mitochondrial function. There were energy buffers, antioxidants, amino acids restoring nitric oxide production, agents enhancing Mitochondrial biogenesis and other drugs [47]. A large number of treatments are already being used in the diseases mentioned in the second point above. (1) Urolithin has been found to have good oral safety and can exhibit antioxidant activation, clear excess ROS, treat chronic diseases such as neurodegenerative diseases, diabetes, cancer, cardiovascular disease, etc. [48]; (2) Nutraceuticals can be used to treat bipolar disorder; (3) Metformin can regulate glucose homeostasis, is one of the safest and most effective anti-hyperglycaemic agents employed as first-line oral therapy for T2D, but it can cause gastrointestinal disturbances [49]; (4) Gastrointestinal disorders caused by mitochondrial diseases can be treated with drugs such as glucose, domperidone, amitriptyline, etc. and in severe cases surgical resection can be performed [50]; (5) Inhibition of mitochondrial fatty acid oxidation was a treatment of heart failure, ischaemic heart disease and diabetic cardiomyopathy. Such as MCD inhibitors, CPT-1 inhibitors [51]. However, this type of treatment was relatively difficult, and the drug will have a certain negative effect. Therefore, this aspect was still a huge challenge.

The above three aspects were the hot spots in the research field of mitochondrial dysfunction in the past 20 years, and the main hot spots vary from one to the other, as shown in Figure 9. Since 2002, we have detected the 25 keywords high outbreak.

5. Strengths and Limitations

Our study used four pieces of software for analysis, two of which (VOSviewer and CiteSpace) have been widely used in the scientometric field. Thus, the data analysis process may be objective. Because cite space can only retrieve data from WOSCC and can only identify English literature, some sources of literature cannot be identified by CiteSpace, so there may be discrepancies between our results and the overall publication.

Publications on mitochondrial dysfunction have been increasing over the past 20 years, and since the search for literature was in May 2022, the 2022 article was not comprehensive, but the general trend can still be predicted. The current work studies the overall trend of mitochondrial dysfunction, and future studies in a specific area of mitochondrial dysfunction can help solve most of the currently existing diseases.

6. Conclusion

Mitochondrial dysfunction was related to a variety of pathogenesis, and because there were many triggers for mitochondrial dysfunction, it was a major problem in the treatment of such diseases. Because the research on this field has taken a long time, some of the corresponding basic distances have been mastered, but there was currently less research on the emerging field of mitochondrial apoptosis, and this aspect should be studied in depth. Near-mitochondrial dysfunction was thought to be associated only with inherited mitochondrial disease, targeting mitochondrial dysfunction by various strategies was a huge challenge. At the same time, how to apply mitochondrial dysfunction to clinical cases was also a challenge. The metabolism, vascular, cardiac, neurodegenerative diseases and cancer were many things to be improved.

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