

Received: 2018.10.15

Accepted: 2018.11.06

Published: 2018.11.20

Scientometric Analysis of SIRT6 Studies

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Source of support: This work was supported in part by National Natural Science Foundation of China (81672523, 81472403, 81472404, 81272834, 81472403)

Background: SIRT6 is a molecule of significant interest in the field of epigenetics. This review of the literature aimed to explore research hotspots and other bibliometric features of SIRT6 by applying several bibliometric analysis tools and by establishing a comprehensive scientometric analysis model of SIRT6.


Material/Methods: The research sample included 441 articles related to SIRT6 obtained from the Web of Science core collection. Bicom software was used to extract high frequency keywords, and then a binary matrix and a co-word matrix were constructed. We used Gcluto for double clustering, EXCEL for strategic coordinate building, Citespace software for co-citation analysis, CitNetExplorer for citation analysis, and Vosviewer for journal and term analysis.

Results: Research hotspots and the base knowledge of SIRT6 were determined by co-word and co-citation network analysis. The strategic coordinates approach was used to assess the research prospects of each hotspot and the connections between these hotspots. The distribution of disciplines and journals was determined and both a term density map and a dual-map were constructed by application of different tools.

Conclusions: SIRT6's regulation of chromatin, lifespan, DNA damage, and metabolism make up the most important SIRT6 intellectual basis from the past 10 years. SIRT6 study has concentrated on the effects of this molecule on tumors and shown promising trends in understanding neural diseases. However, there has been little analysis of how SIRT6 effects are part of more complex systems. Work by Motoslavsky (2006) represents a milestone in SIRT6 research, and the studies by Kawahara 2009 and Kim 2010 are key in the knowledge transmission of SIRT6 research.

MeSH Keywords: **Bibliometrics • Computational Biology • Histone Deacetylases • Sirtuins**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/913644>

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Background

The field of epigenetics has experienced remarkable research attention in recent years and there have been major advances in elucidation of how histone modification can regulate gene expression. Proteins in the sirtuin family are highly conserved from bacteria to humans. These proteins play an important role in epigenetic regulation [1] and are class III histone deacetylases (HDACs) [2]. The sirtuin family has 7 homologs in mammals, proteins SIRT1–SIRT7. SIRT6 is mainly located in the nucleus, highly expressed in bones and ovaries, and shows almost no expression in marrow [3]. The human SIRT6 gene is located on chromosome 19p13.3. This region of the chromosome has been identified as a hotspot for mutation in many tumor diseases, according to data from the CGAP (Cancer Genome Anatomy Project) and NCI (National Cancer Institute) databases [4]. SIRT6 is a HDAC and a homolog of sir2, silent information regulator-2, which plays a key role in transcription silencing in *Saccharomyces cerevisiae* [5]. SIRT6 plays important roles in gene regulation, DNA damage repair, glucose metabolism, and tumor genesis [6]. SIRT6-deficient monkeys die several hours after birth and exhibit severe prenatal developmental delay [7]. Current methods to study the function of a specific protein mainly include cellular, molecular biological, and biochemical approaches, bioinformatic analysis, and omics analysis. However, very few researchers utilize systematic bibliometric analytical approaches to study a specific protein or gene. Recent studies indicate that SIRT6 affects a variety of biological processes. However, bibliometric analysis of SIRT6 has not been performed and could potentially provide additional insight into how this protein works in cells.

Many bibliometric analysis methods and tools have been developed to help researchers in different fields construct knowledge maps and evaluate the collective state of thought about a subject and identify hotspots in a research field. The 2 most common methods are co-word and co-citation analysis. Co-word analysis is an important bibliometric analysis method that helps researchers identify the hot topics and trends in a discipline [8]. In an article, if 2 words co-occur frequently, they may have a closer relationship than other pairs of words [8]. The citations in an article can provide important insight into what is currently known for a given topic. The most common method to acquire this information is by co-citation analysis: 2 papers that are both cited by a third article have a co-citation relationship. Statistical analysis of the strength of this relationship between articles can help researchers identify the intellectual base of the discipline, research frontiers, important authors, and other bibliometric information [9–11].

Due to the abstract features of information in a text, visual analysis is often used in bibliometric studies, using visualization tools such as Citespace, Vosviewer, Bicom, and BibExcel [9–11].

These tools can be used to perform bibliometric analysis of a topic from a variety of perspectives, such as co-word analysis, co-citation analysis, and author and institute distribution analysis. For example, Lu et al. used Bicom to analyze the hotspot distribution of topics in tumor immunotherapy by co-word analysis [12]. Chen et al. used Citespace to analyze the bibliometric characteristics of the regenerative medicine field and predict future research trends [13,14]. In the life sciences, researchers may perform a bibliometric analysis of a single research topic or a specific disease. However, bibliometric analyses are not typically performed for the analysis of a single gene or protein. This study was the first to apply a variety of tools to comprehensively analyze the state of SIRT6 research, revealing the bibliometric features of the SIRT6 research topic from various perspectives. The results enabled clarification of the state of the field and current research hotspots for SIRT6, and identified important research and researchers in this field. This focus on SIRT6 enabled us to establish an effective model of single gene/protein bibliometric comprehensive analysis. This model can be applied to other single genes or proteins to identify achievement in the field and evaluate the publication record of research institutions to guide research strategies and funding decisions.

Material and Methods

Data collection

This study searched the Web of Science Core Collection (WoSCC) for relevant articles. We obtained articles about SIRT6 published from January 1, 2000 to April 28, 2018. The search identified 441 articles, and the titles, keywords, author information, abstracts, and references were downloaded and stored in TXT format.

Co-word analysis

Data extraction and matrix construction was performed using Bicom software to extract the keywords from the set of SIRT6-related articles obtained from the WoSCC as described. Bicom allowed extraction of high-frequency keywords, which generated a binary matrix of word-paper (Table 1) and a co-word matrix (Table 2) based on high-frequency words. These 2 matrices were then used for double-cluster analysis and to build strategic coordinates [15]. Double-cluster analysis was performed using Gcluto. Gcluto is a matrix double-clustering visualization analysis toolkit [16]. We used Gcluto to double-cluster the binary matrix to summarize the hotspot categories. Additionally, we used Gcluto to build a mountain map and a heat map based on the results of the double-clustering analysis.

The strategic coordinate approach was first proposed by Law et al. [17]. It is a set of 2-dimensional coordinates with 4

Table 1. Binary matrix of high frequency keywords and SIRT6 articles.

No.	Keyword	Paper ID				
		001	002	003	...	435
1	Sirt6	1	1	1	...	0
2	Sirtuin	0	0	0	...	0
3	Aging	0	0	0	...	1
4	Cancer	0	1	0	...	0

29	Atherosclerosis	0	0	0	...	0
30	Differentiation	0	0	0	...	0

Table 2. Co-word matrix of high frequency keywords of SIRT6 articles.

No.	Keyword	Sirt6	Sirtuin	...	Differentiation
1	Sirt6	130	12	...	2
2	Sirtuin	12	75	...	2
3	Aging	13	16	...	0
4	Cancer	17	5	...	0
...
30	Differentiation	2	2	...	4

Table 3. The centrality and density of the eight clusters.

Cluster	Intra-class link averages	Density-Y	Inter-class link average	Centrality-X
0	4.833333333	2.760416667	6.728395062	5.05000095
1	1	-1.072916667	2.086419753	0.408025641
2	3.833333333	1.760416667	1.234567901	-0.443826211
3	2.5	0.427083333	0.975308642	-0.70308547
4	2.166666667	0.09375	0.817307692	-0.86108642
5	0.75	-1.322916667	0.721153846	-0.957240266
6	1.15	-0.922916667	0.464	-1.214394112
7	0.35	-1.722916667	0.4	-1.278394112
Average	2.072916667		1.678394112	

quadrants, with an x-axis and a y-axis. This approach uses the co-word matrix to calculate the intra-class link averages and the inter-class link averages of each hotspot category (Table 3). Next, the centrality X and the density Y are calculated, and used to establish the strategic coordinates. The greater the centrality X of a category, the greater its intensity of interaction with other categories. The greater the density Y of a category, the stronger its internal integration.

High-frequency keyword visualization was performed using the Foamtree online system to generate a word-cloud based on PubMed. Vosviewer (version 1.6.8), a computer program for bibliometric data visualization [18], was used for high-frequency term and time fusion analyses and to create a keyword density map.

Co-citation analysis

Citespace (version 5.2R2) software was used for co-citation analysis. Citespace is a bibliometric analysis visualization software developed by Chen [11,19]. We imported the full dataset of 441 SIRT6 articles into Citespace and set the time slicing as “2008–2018”. the years per slice was set as “1” and the 50 most highly cited papers were selected for each time slice. These selections were used to construct a co-citation literature network containing 254 nodes, where each node is a cited paper and the network “E” has a connection number of 915. After construction of the initial co-citation network, cluster analysis, citation burst detection, and timeline or time zone view were applied. Citation network analysis used CitNetExplorer is a literature citation relationship analysis tool that can sort the citation relationships of important articles in a domain in chronological order [20]. CitNetExplorer was used to construct a citation network. After importing the experimental dataset into CitNetExplorer, the top 50 most cited articles were selected for citation network construction. Discipline and journal analysis were performed using Vosviewer for journal co-citation density analysis and Citespace for journal dual-map overlay analysis.

Results

Co-word analysis

The overall work flow is shown in Figure 1A. The literature search identified 441 articles on SIRT6, and 799 keywords were extracted using the Bicom software. After analysis and discussion, the top 30 most frequent words were selected as high-frequency keywords (Table 4). Based on these high-frequency words, a binary matrix (Table 1) and a co-word matrix (Table 2) were constructed. We used the Foamtree online system to obtain the high weight retrieval result distribution to construct a hot topic word cloud for both the sirtuin family (Figure 1B) and SIRT6 (Figure 1C) in PubMed. At the same time, we used Vosviewer to generate a fusion view of the SIRT6 high frequency keywords over time and a high frequency keyword density view (Figure 1D, 1E).

Gcluto was used to visualize the double clustering results for the binary matrix (Table 1) and then generate a mountain map (Figure 2A) and a heat map (Figure 2B). As shown in Figure 2A, each cluster was assigned a label of 0–7 and the height, volume, and the color of each peak indicated detailed information for each cluster. The volume of the mountain indicated the number of keywords in the cluster. The distance between peaks represented the similarity of the 2 clusters. The color of the peak represented the standard error of each cluster, with red representing a high value and blue representing a low value. In Figure 2B, each row represented a high frequency keyword

and each column represented the corresponding article. The color of the cell reflected the frequency of occurrence, where the higher the frequency, the deeper the color. The double clustering parameters are shown in Table 5. Based on the semantic connections between high-frequency words and the source articles of high-frequency words, we clustered the high-frequency words for SIRT6 into the following 8 hot topics.

- Cluster 0: The effects of sirtuin family members on metabolism and aging.
- Cluster 1: The role of SIRT6 in cell proliferation and differentiation in neurological diseases, tumors, and aging.
- Cluster 2: Epigenetic regulation of SIRT6.
- Cluster 3: Regulation of SIRT6 in DNA damage repair and metabolism.
- Cluster 4: Interaction of SIRT6 with cancer and microRNA interactions.
- Cluster 5: The effect of SIRT6 on DNA damage and its association with exercise.
- Cluster 6: SIRT6's function on life, P53, NF-kappa B, and energy limitation.
- Cluster 7: SIRT6's role in oxidative stress, diabetes, autophagy, inflammation, and atherosclerosis.

Next, we calculated the centrality and the density of each topic through the co-word matrix (Table 3) combined with the aforementioned 8 hot topics and then established strategic coordinates based on the data (Table 3, Figure 2C). In the strategic coordinates (Figure 2C), the x-axis represents centrality and the y-axis represents density. As shown in Figure 2C, the strategic coordinates have 4 quadrants and the deeper the red, that is, moving toward the axis, the greater the centripetal nature and density, and the deeper the blue, that is, moving against the axis, the lower the value of these 2 parameters. In the strategic coordinates, the first quadrant represents a relative core and mature hot field, the second quadrant represents a peripheral mature domain, the third quadrant represents isolated and unpopular fields, and the fourth quadrant represents potential developing fields. Typically, analyses are most interested in new and exciting topics in the fourth quadrant [12].

Co-citation analysis

The co-citation analysis assesses if articles are cited together and their corresponding frequencies and scales. If 2 articles are both cited as references in another article, then those 2 papers have a co-citation relationship [21]. Here, Citespace was used to build a co-citation network for SIRT6 research articles. The network of articles represents the intellectual basis of the field (Figure 3A). In the initial network (Figure 3A), we represent literature nodes in the form of an “annual ring map.” The radius of a node corresponds to its frequency, where a larger radius corresponds to a higher local citation in

Table 4. High frequency keywords in SIRT6 research.

No.	Key words	Frequency n (%)	Cumulative percentage, %
1	Sirt6	130 (9.6083)	9.6083
2	Sirtuin	75 (5.5432)	15.1515
3	Aging	36 (2.6608)	17.8123
4	Cancer	29 (2.1434)	19.9557
5	Oxidative Stress	18 (1.3304)	21.2860
6	Sirtuin1	17 (1.2565)	22.5425
7	Acetylation	15 (1.1086)	23.6511
8	Inflammation	14 (1.0347)	24.6859
9	Apoptosis	13 (0.9608)	25.6467
10	NAD	13 (0.9608)	26.6075
11	Epigenetics	12 (0.8869)	27.4945
12	Metabolism	11 (0.8130)	28.3075
13	Deacetylation	11 (0.8130)	29.1205
14	Brain	10 (0.7391)	29.8596
15	Diabetes	9 (0.6652)	30.5248
16	calorie restriction	8 (0.5913)	31.1160
17	Longevity	7 (0.5174)	31.6334
18	DNA damage	7 (0.5174)	32.1508
19	Autophagy	7 (0.5174)	32.6681
20	Glycolysis	6 (0.4435)	33.1116
21	DNA repair	6 (0.4435)	33.5551
22	microRNA	5 (0.3695)	33.9246
23	NF-kappa B	5 (0.3695)	34.2942
24	p53	5 (0.3695)	34.6637
25	Sirtuin3	5 (0.3695)	35.0333
26	Sirtuin7	4 (0.2956)	35.3289
27	Proliferation	4 (0.2956)	35.6245
28	Exercise	4 (0.2956)	35.9202
29	Atherosclerosis	4 (0.2956)	36.2158
30	Differentiation	4 (0.2956)	36.5115

the co-citation network. The annual ring for each node represents a different year, and the more citations for an article, the wider the annual ring. Citespace typically uses red and purple circles to represent nodes with special attributes [13]. A red circle indicates a burst of citations at a certain time. In addition, if the betweenness centrality of a node is greater than 0.1, meaning that the node has links with over 10% of the nodes in the whole network, then the node will have a purple circle [14,22]. In the network, the links between nodes represent the co-citation relationship between the nodes, where the thickness of the link is proportional to the co-citation strength. The color of the line indicates the time period in which the

co-citation first occurred. In the co-citation network for SIRT6 shown in Figure 3A, 2 nodes have purple circles, Kawahara et al. (2009) [23] and Kim et al. (2010) [24]. The study by Kawahara et al. revealed that SIRT6 acts on chromatin and attenuates NF-κB signaling pathways to affect premature aging and normal aging [23]. The work by Kim et al. revealed that SIRT6 regulates hepatic glucose metabolism and lipid metabolism [24]. These 2 nodes have a high betweenness centrality in the network, indicating that these nodes may bridge different knowledge areas. In this initial network, nodes with radii significantly larger than that of other nodes are considered landmark nodes, articles with more significant influence for that

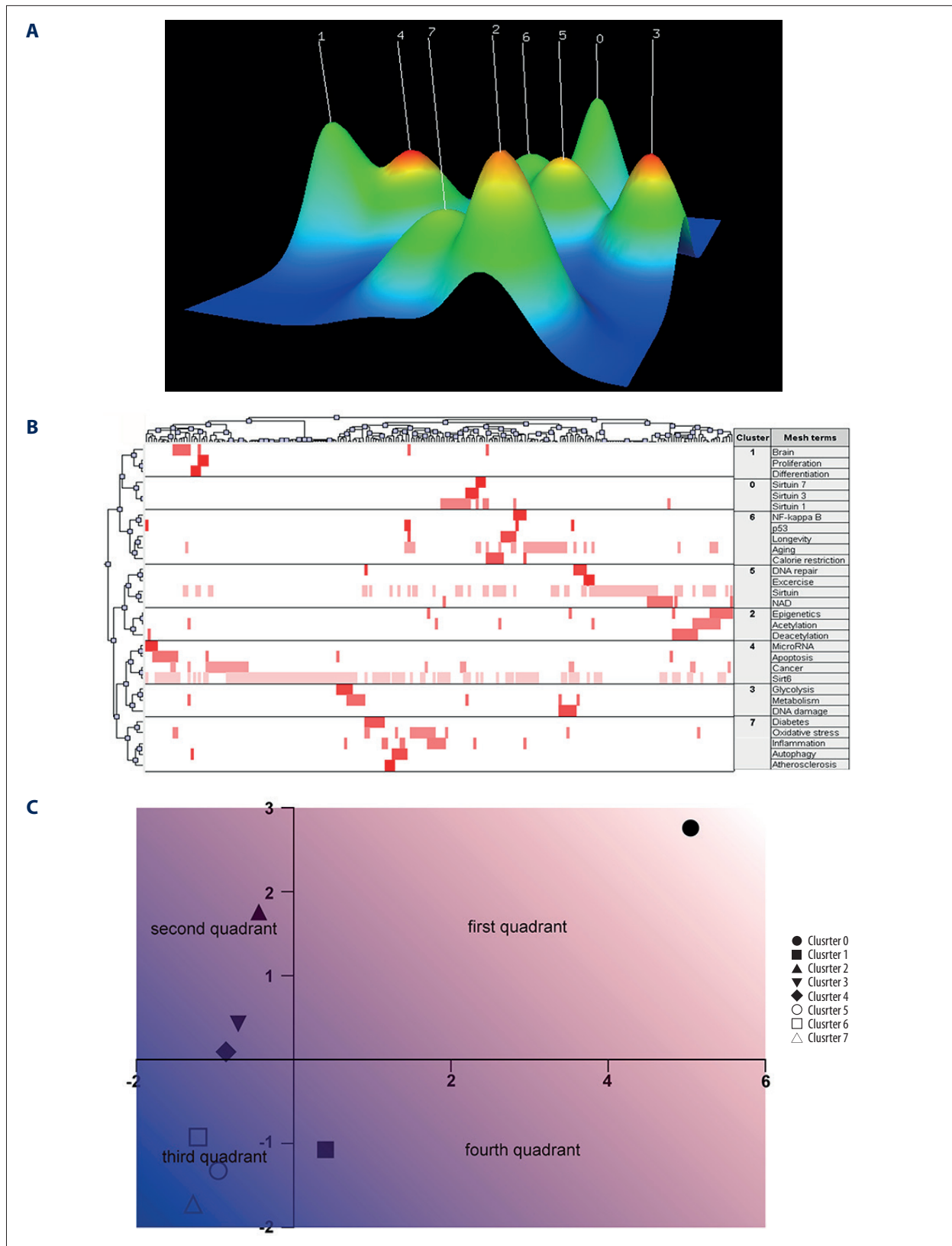


Figure 2. (A) Mountain visualization of biclustering of highly frequent keyword and SIRT6 articles. (B) Visualized matrix of the biclustering of high frequency keywords and SIRT6 articles. (C) Strategic diagram of clusters.

Table 6. Twelve research articles corresponding to the landmark nodes in the co-citation network.

Node's name	Node's type	Title	Journal
Kawahara Tla (2009)	Pivot & land mark	SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span	Cell
Kim Hs (2010)	Pivot & land mark	Hepatic-specific disruption of SIRT6 in mice results in fatty liver formation due to enhanced glycolysis and triglyceride synthesis	Cell Metabolism
Mostoslavsky R (2006)	Land mark & burst	Genomic instability and aging-like phenotype in the absence of mammalian SIRT6	Cell
Michishita E (2009)	Land mark & burst	Cell cycle-dependent deacetylation of telomeric histone H3 lysine K56 by human SIRT6	Cell Cycle
Zhong L (2010)	Land mark	The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha	Cell
Michishita E (2008)	Land mark	SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin	Nature
Sebastian C (2012)	Land mark	The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism	Cell
Kanfi Y (2012)	Land mark	The sirtuin SIRT6 regulates lifespan in male mice	Nature
Mao Zy (2011)	Land mark	SIRT6 promotes DNA repair under stress by activating PARP1	Science
Kaidi A (2010)	Land mark	Human SIRT6 promotes DNA end resection through CtIP deacetylation	Science
Jiang H (2013)	Land mark	SIRT6 regulates TNF- α secretion through hydrolysis of long-chain fatty acyl lysine	Nature
Sundaresan Nr (2012)	Land mark	The sirtuin SIRT6 blocks IGF-Akt signaling and development of cardiac hypertrophy by targeting c-Jun	Nature Medicine

area of research. In addition to the 2 pivotal nodes described above, ten other significant landmark nodes were identified and are listed in Table 6. Of these, the landmark node corresponding to Zhong et al. (2010) [25] has the largest radius, indicated the highest frequency number in the co-citation network. The article corresponding to this node showed that SIRT6 regulates glucose homeostasis through HIF1a [25]. The 2 red nodes corresponding to Mostoslavsky et al. (2006) [26] and Sundaresan et al. (2012) [27] have cited number bursts. Mostoslavsky et al. found that SIRT6 limits DNA damage and plays a role in aging [26]. Sundaresan et al. reported that SIRT6 attenuates the IGF-AKT signaling pathway [27].

Clustering analysis of SIRT6 co-citation network

The literature represented in the co-citation network was then organized into 8 different clusters, as shown in Figure 3B. The clusters are named by extracting nominal terms as tags from the titles of the cited articles. The LSI (latent semantic indexing) algorithm was used as the extraction method. As shown in Figure 3B, the co-citation literature network for SIRT6 was divided into 8 categories. By combining the tags and then studying the articles corresponding to each category of nodes and articles that cite these articles, the main intellectual structure and the current state of research in the SIRT6 research

field can be determined [28]. In this way, we conclude that the current intellectual base of SIRT6 research is as follows.

- Cluster 0 (chromatin localization): A study of the biological function and roles of SIRT6, including telomere chromatin, longevity (aging), DNA damage, and metabolic activities to regulate other biological processes.
- Cluster 1 (Sirt6 deficiency): The biological function of other members of the sirtuin family, primarily SIRT3.
- Cluster 2 (DNA repair): The biological function of other members of the sirtuin family, primarily SIRT1.
- Cluster 3 (human sirtuin): Studies of the biological effects of SIRT6.
- Cluster 4 (poor prognosis): The role of SIRT6 in a variety of cancers.
- Cluster 5 (myocardial infarction): SIRT6's roles in autophagy, microRNA, cholesterol metabolism, and other regulatory processes.
- Cluster 6 (microRNA modulation): SIRT6 regulation of liver metabolism.
- Cluster 7 (mammalian model): SIRT6 regulation of the cardiovascular system.

Table 7. The top 10 citation burst strength articles in the co-citation network.

No.	Strength	Title	Author
1	25.8634	Genomic instability and aging-like phenotype in the absence of mammalian SIRT6	Mostoslavsky R
2	10.9921	Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins	Michishita E
3	10.9921	Mouse Sir2 homolog SIRT6 is a nuclear ADP-ribosyltransferase	Liszt G
4	4.9675	Sirtuins in mammals: insights into their biological function	Michan S
5	4.634	Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase	Cohen HY
6	4.1378	Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1	Rodgers JT
7	3.7595	Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha	Lagouge M
8	3.2896	Increased dosage of a sir-2 gene extends lifespan in <i>Caenorhabditis elegans</i>	Tissenbaum HA
9	2.6305	hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase	Vaziri H
10	2.6305	DNA repair, genome stability, and aging	Lombard DB

Citation burst detection

We used Citespace software to analyze the co-citation network and obtained the top 10 citation bursts, as shown in Figure 3C. The number of citations of these articles suddenly increased in a certain period of time after publication, indicating the rapid acceptance and dissemination in the field of the presented research results, making a significant contribution to the knowledge structure [13]. Examples of the topics of these articles showing bursts include the resistance of SIRT6 to DNA damage [26], the nuclear ADP-ribosyltransferase of SIRT6 [29], the subcellular localization and function of SIRT1–SIRT7 [30], autophagy [31], and inflammation regulation [32]. The highest citation burst strength for Mostoslavsky et al. (2006) [26] with the longest duration indicated its significant impact on the SIRT6 field. The articles with the 10 highest citation burst strengths are listed in Table 7.

Timeline view and time zone view of SIRT6 co-citation network

A timeline view can help show changes in the research trends in a field with time. As shown in the timeline view presented in Figure 4A, nodes of a cluster share a horizontal line. The publication dates of articles are placed at the top of the view, with the most recent articles positioned closer to the right. The timeline view clearly shows the number of nodes in each cluster. The number of nodes in a cluster reflects the importance of that field, where a higher number of nodes correlates to higher importance. This view also allows visualization of the most important articles in a particular subfield, and shows the emergence,

popularity, and decline of research topics. Additionally, this view shows the temporal characteristics of the research areas reflected by clustering. It can be seen from Figure 4A that the development of cluster 2 (DNA repair) occurs first, indicating that early studies of SIRT1 focused on DNA repair. Cluster 4 (poor prognosis) and cluster 5 (myocardial infarction) developed later, possibly because they reflect the further development of the early intellectual base (clusters 0, 1, and 2).

Differently than the timeline view, the time zone view (Figure 4B) aggregates simultaneous nodes at the time when articles are first cited by the co-citation network. Through this visualization, the evolution of the SIRT6 domain for a certain segment of time can be clearly demonstrated. The presence of more articles for a certain time zone indicates an important time period with influential results. In contrast, fewer articles indicate a time period with fewer influential results. The node links between time zones indicate the inheritance of the knowledge, or to what extent the knowledge was accepted, inspired subsequent research, and led to additional findings. For example, Frye et al. (2000) is marked with a star mark in Figure 4B; this article first identified human SIRT6 [32]. The node for Mostoslavsky et al. (2006) [26] is the earliest landmark node. After publication of this work, many additional landmark nodes emerged in the field.

Citation analysis

We next used CiteNetExplorer to construct a citation network view of SIRT6. We analyzed the development of the 50 most cited articles about SIRT6 (Figure 5A). The curves between

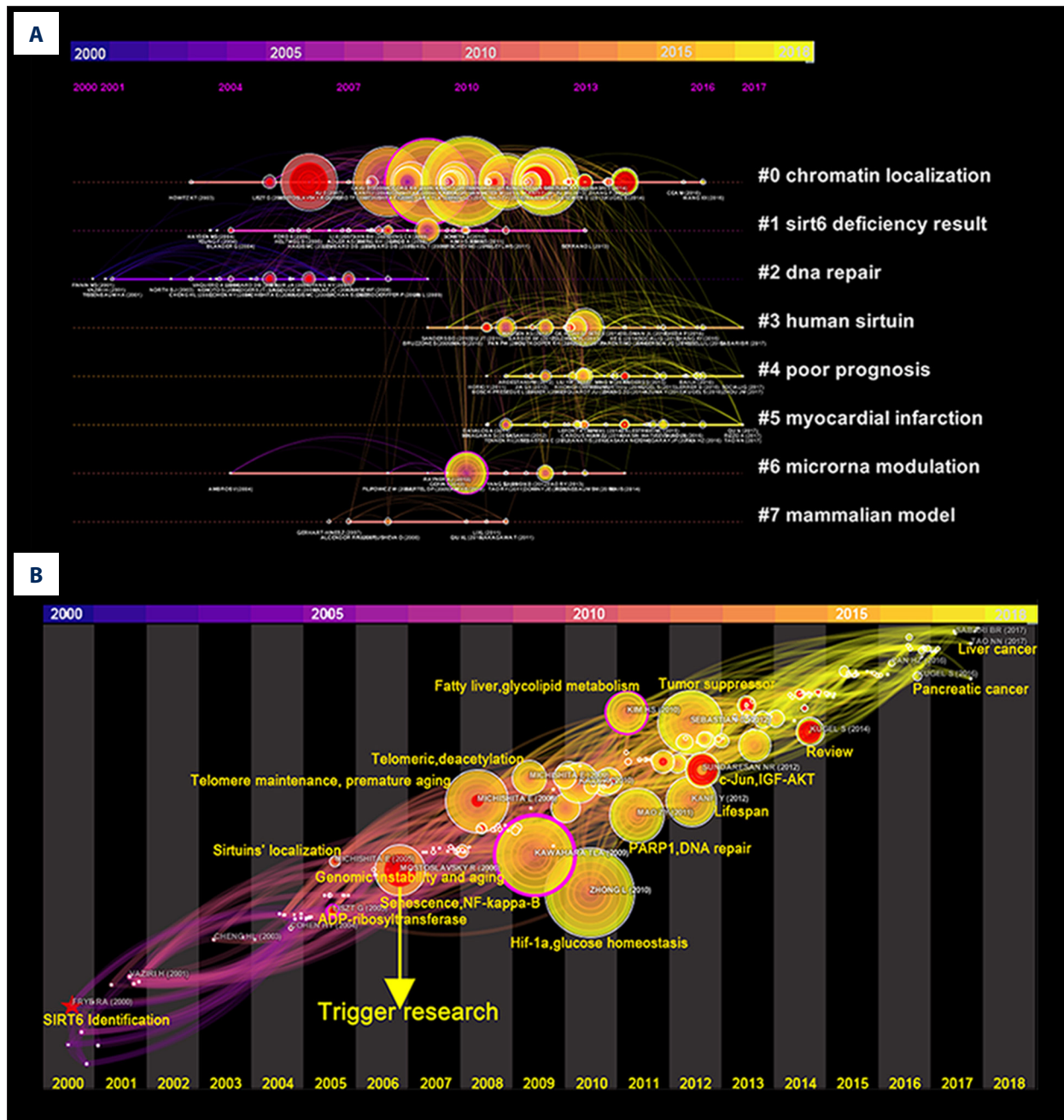


Figure 4. (A) Timeline visualization from 2008 to 2018. (B) Time zone visualization from 2000 to 2018 is shown, some nodes are labeled with corresponding topics.

the nodes represent the citation relationships, and the cited articles are presented below the citing papers. To annotate the citation network shown in Figure 5B, each node was labeled with the first letter of the node name and the major topic of the article. The citation network allows readers to more easily visualize the development of SIRT6 research over time. As shown in Figure 5, the important nodes in the co-citation network are positioned closer to the core of the citation network and have more citation connections.

Discipline and journal analysis

Dual-mapping analysis (Dual-Map Overlay) was designed by Chen and Leydesdorff to reveal overall scientific contributions [34]. Dual-map overlays show the interactions of more than 10 000 journals. These journals are further divided into different areas so that the publications and citations of this domain can be depicted at the disciplinary level. In order to visualize a more comprehensive view of the citation state of

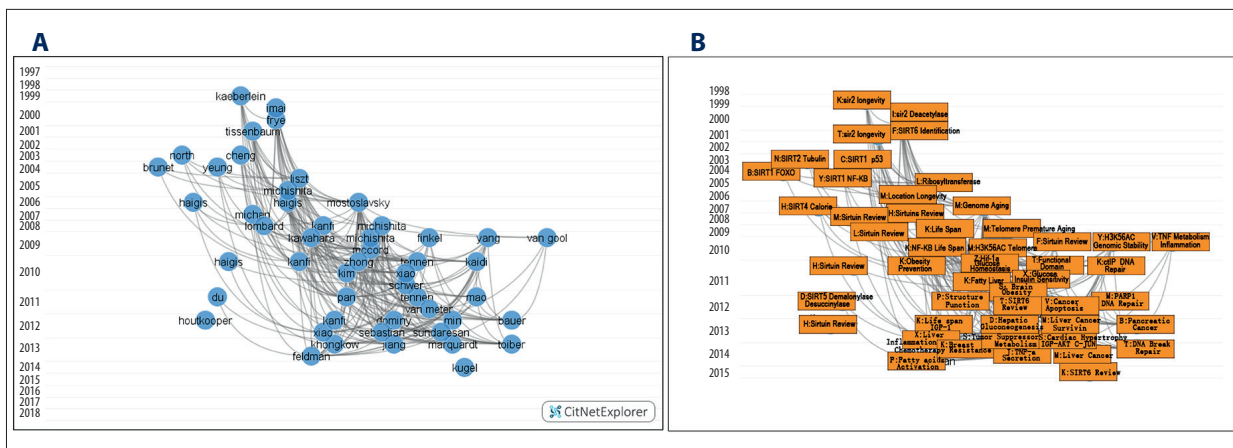


Figure 5. (A) Citation network of the 50 most cited articles. (B) Explanation of the citation network.

SIRT6, we constructed a citation dual-map using Citespace's dual-map overlay function. As shown in Figure 6A, the left half side is the citing map, the right half side is the cited map, and the curve is the citation path connection line from the left side to the right side. This connection illustrates the flow of knowledge and connections in different areas of research. Figure 6B shows the density map of the co-citation journals, indicating the density distribution of journals that provide the intellectual base for SIRT6 research. The red indicates the greater density of a journal, and blue indicates a journal with lower density. From this figure, it can be seen that journals such as Cell, Nature, and Journal of Biological Chemistry are the most influential sources of knowledge in the field of SIRT6.

Discussion

This study explored the bibliometric characteristics of SIRT6 research by applying a variety of scientometric tools. We analyzed an epigenetic-related protein from a bibliometric perspective for the first time and extended the application range of bibliometric analysis. Through co-word analysis and co-citation analysis, we identified hotspots of SIRT6 research, its intellectual base, and analyzed its historical development. Importantly, this is the first bibliometric analysis model of a single gene or protein (Figure 1A).

Co-word analysis was performed to visually present hotspots of the SIRT6 research domain and to construct strategic coordinates. In the analysis of strategic coordinates (Figure 2C), research hotspots of SIRT6 were distributed in each quadrant. Category 0 (effects of sirtuin family members on metabolism and aging) was located in the first quadrant, had intense interaction with other clusters, and a high degree of internal integration. Cluster 1 (role of SIRT6 in cell proliferation and differentiation in neurological diseases, tumors, and aging) was located in the fourth quadrant, indicating a core but

immature field. This quadrant is likely the most promising field. The effects of SIRT6 on neurological diseases have not received as much attention as the effects on tumors and aging, and this may indicate a potential promising hotspot [35]. Clusters 2, 3, and 4 were located in the second quadrant, indicating that these 3 categories are loosely connected to other categories, but had strong internal integrity. This indicated accumulated knowledge about SIRT6 in the fields of tumors, microRNAs, etc., but this knowledge was not fully linked to other clusters of SIRT6 studies. Clusters 5, 6, and 7 were in the third quadrant, indicating immature and peripheral fields. They were loosely connected with other clusters, and had low internal integration. This indicated that the topics corresponding to these 3 clusters were relatively isolated, and were difficult to link to other topics. From Figure 1B, SIRT1 and SIRT3 were found to have a higher weight in the sirtuin family, probably because they were found earlier so there were more related publications. As shown in Figure 1D, the SIRT6 keyword with the highest density was lifespan, suggesting SIRT6's potential role in affecting lifespan is the most important topic of SIRT6 research (Figure 1D).

Co-word analysis is a micro-analysis method to determine the research hotspots of a topic and intuitively display the findings. However, the citations of an article are also informative, as they indirectly reflect the important concepts of a particular topic. Co-citation analysis identified 8 main intellectual bases in SIRT6 research. We found that the sirtuin family is a research hotspot and also an important intellectual base in this field, which makes sense given that the study of a particular molecule is often influenced by research about its family members as they may share biological functions [36,37]. The time zone view in Figure 4B combined with the citation burst detection in Figure 3C indicated that the work of Mostoslavsky 2006 [26] had the greatest impact on the field, with its largest citation burst strength, 25.8634. This article was also the earliest landmark node in the time zone view. Other significant

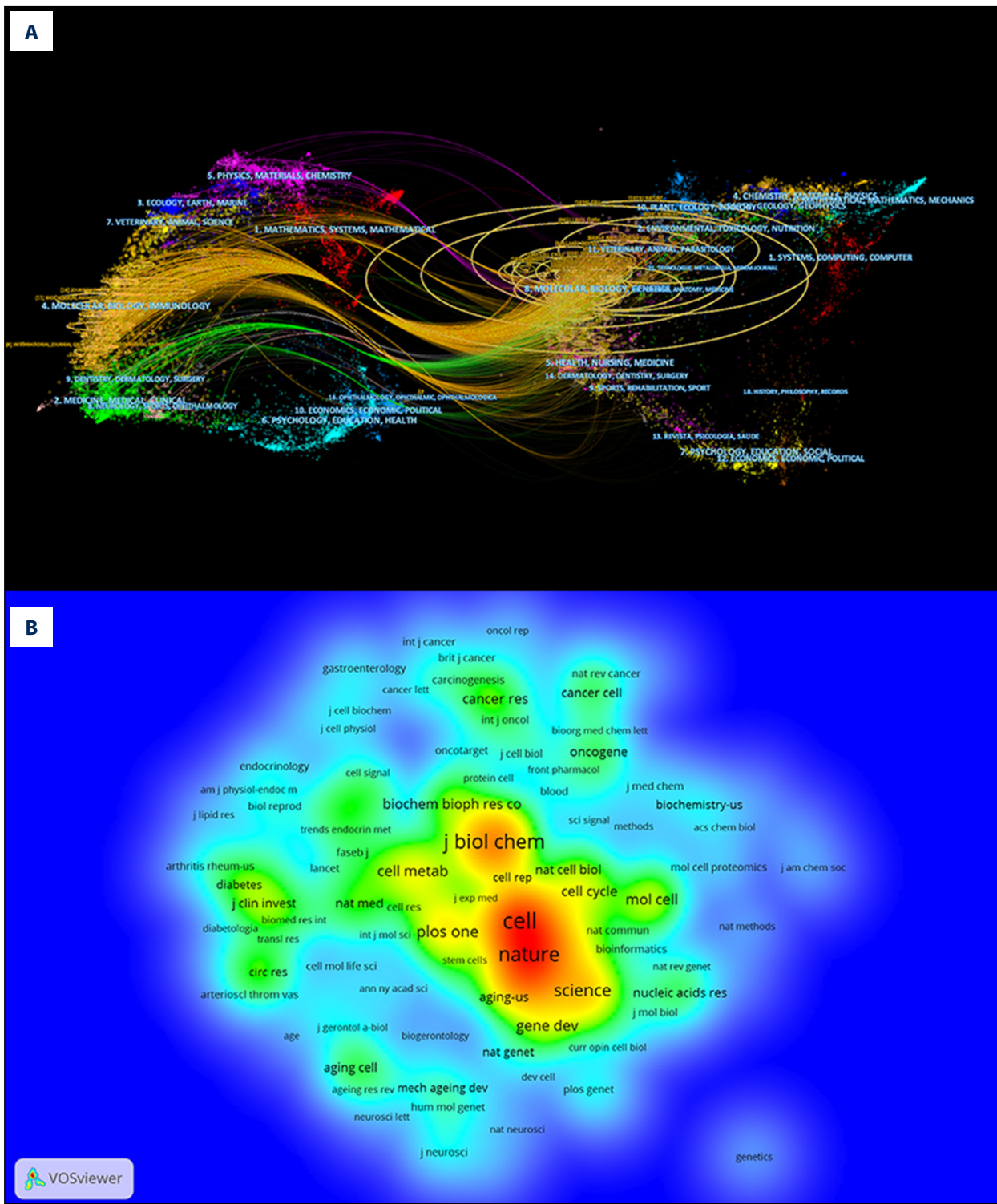


Figure 6. (A) Dual-map overlays of SIRT6 articles. (B) Journal density map based on co-citation.

nodes occurred later, and thus we refer to the Mostoslavsky (2006) [26] study as “trigger research” which may have triggered other major breakthroughs or scientific activities. The Mostoslavsky (2006) article reported the establishment of a

SIRT6 knockout mouse model with many aging-related phenotypes, providing clues into the potential function of SIRT6 [26]. This type of work can promote further research and publications, as the development of an innovative gene knockout

animal model facilitates subsequent experiments, making it a pioneering study in a field.

The co-citation network (Figure 4A) revealed the importance of the articles from Kawahara (2009) and Kim (2010) with more co-citation links than other published articles in the co-citation network of SIRT6. Therefore, these 2 articles may have pivotal roles in the process of knowledge inheritance and transmission. The Kawahara (2009) study revealed the mechanism of SIRT6 in cell senescence regulation and the role of NF- κ B, a key transcription factor involved in multiple disease states [39]. Kim (2010) developed an innovative animal model to explore SIRT6 effects in metabolism, using a variety of genes and tissue types [38]. In addition to innovative academic significance, the novelty and diversity of the research content may explain the importance of these works.

Analysis presented in Figure 1E and Figure 4B shows that in recent years, the focus of SIRT6 research has gradually shifted from aging to the field of cancer. This shift may be because many pathological processes associated with aging also contribute to tumorigenesis, as proteins that regulate longevity and aging may also act in tumorigenesis [40,41]. From the time zone view, we see few significant nodes at the later end of the time zone. However, this is expected, because co-citation and citation analysis lack sensitivity to recent research

without subsequent articles that can cite the work. In the dual-map overlay analysis (Figure 6A), we determined that SIRT6 is limited to the fields of medicine and biology, but little has been done related to other disciplines. Thus, cross-disciplinary research on SIRT6 may be a potential development opportunity for SIRT6.

Conclusions

Co-word analysis and co-citation analysis of articles about SIRT6 were performed using various scientometric tools to reveal the bibliometric characteristics of SIRT6 research. We found that the most important intellectual basis over the past decade for SIRT6 includes the regulation of chromatin, lifespan, DNA damage, and metabolism. Although most studies of SIRT6 have been isolated with little attempt to look at the combined research of SIRT6 to other disciplines, there have been promising trends to understand role of SIRT6 in neural diseases. The article by Motoslavsky (2006) served as a milestone for SIRT6 research and articles by Kawahara (2009) and Kim (2010) served pivotal roles in the knowledge transmission of SIRT6 research. Future bibliometric analysis of members of the sirtuin family should explore the interactions between family members as well as the overall scientometric characteristics of the whole sirtuin family.

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