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Original Article

Knowledge base and emerging trends in YAP1 research

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Abstract: Yes-associated protein 1 (YAP1) is a transcriptional coactivator that mediates the Hippo signaling pathway, which participates in the development and growth of the body; it plays key roles in tumorigenesis, metastasis, and therapy resistance. However, the pathophysiological mechanism of YAP1 has not been fully elucidated. Therefore, we explored the status and evolutionary trend in YAP1 research via bibliometric analysis. A total of 2,928 publications were downloaded from Web of Science Core Collection (WOSCC). The co-citation network map was drawn via CiteSpace and VOSviewer software. We analyzed the co-authorship networks among countries, journals, and authors, as well as co-occurrence of co-cited references, citation bursts, and keywords in YAP1 research, in order to predict its literature development. The present research evaluates the annual publication trends of YAP1 literature, and the following results were established: research on YAP1 are of steady increase; China present the highest co-citation; the *Journal of Biological Chemistry* (*J Biol Chem*) was the most productive journal, while *Cell press* received the most citations from co-cited references; Among the authors in the overall citations *Bin Zhao* is the most promising collaborator for emerging scholars in this field; and lastly, co-occurrence keyword analysis indicated that the emerging trends in YAP1 research were mainly focused on cancer therapy. We established that projects on YAP1 research is presently in its rapid developmental stage with active global collaboration. In addition, the mechanism and clinical significance of YAP1 in cancer was established as the potential trend of future studies.

Keywords: YAP1, hippo signaling pathway, bibliometric analysis, citation burstiness, CiteSpace, VOSviewer

Introduction

Yes-associated protein 1 (YAP1), the main coactivator of Hippo signaling pathway, plays a vital role in several biological processes, including cell proliferation, contact inhibition, and stemness [1-3]. As a transcriptional coactivator, YAP1 is abnormally expressed in various malignant tumors, such as colon cancer, gastric cancer, hepatocellular carcinoma, etc, and invariably modulates the biological phenotypes of these cancer cells by regulating their downstream genes [4-6]. In a recent study, researchers reported that a novel YAP1 inhibitor (CA3) could markedly inhibit esophageal adenocarcinoma [2]. Therefore, targeting YAP1 may be considered a novel strategy in the treatment of tumors of YAP1 overexpression [7-9]. However, effective inhibitors for YAP1 have not been established, and more fundamental research is required to improve its clinical application.

As an effective statistical and mathematical method, bibliometric analysis can summarize the hotspots and emerging trends in a field [10]. CiteSpace and VOSviewer are conventional tools employed in the mapping of knowledge domains, to visualize co-occurrence or co-authorship networks [11, 12]. Both software packages have been used by scholars to publish numerous articles in various fields, such as biology, medicine, environmental science, among others. These articles will serve as potential resources for scholars who intend to conduct novel or further scientific research.

Bibliometric analysis on YAP1 research has not yet been published. Thus, in this study, VOSviewer 1.6.17 and CiteSpace 5.8 were used to make a bibliometric analysis of Yap1, to objectively estimate the knowledge area and emerging trends of YAP1 research from the aspects as follows: (1) Provision of general information in YAP1 research, such as annual publications, countries, institutions, authors, and journals. (2) Analysis of high-frequency keywords and co-cited reference bursts for research trend prediction. An in-depth comprehension of the current knowledge structure, emerging frontier fields, and hotspots of YAP1 research is vital for its future exploration.

Data and methods

Data collection

The data for bibliometric analysis were obtained from the WOSCC on February 12, 2022. The language was confined to English, and the paper type to original article or review.

Criteria

Publications that met the inclusion criteria (basic and clinical research; research focus on YAP1) were included in this analysis, while unofficial articles, repeated publications, unrelated articles, or/and those published in 2022 were used as exclusion criteria.

Data visualization

CiteSpace was used to analyze the co-occurrence of countries, institutions, co-cited references, and references burstiness. Prior to analysis, some data were reclassified to obtain more accurate information. Illustratively, England, Scotland, Northern Ireland, and Wales were all reclassified into the UK. Moreover, Taiwan and People's Republic of China (PRC) were reclassified into China.

VOSviewer was used to analyze key words co-occurrence and cluster map. In keyword analysis, we merged certain terms, such as "YAP1" and "Yes-associated protein 1". The time gap was from 1999-2021.

Statistical analysis

As previously mentioned, CiteSpace was used for country, institution, author, and references/keywords burstiness analyses [13]. The size of a node represents the frequency, and the links between each country indicate co-occurrence relationships. Clustering analysis of keywords co-occurrence and frequency statistics were performed via VOSviewer [14]. Overlay visualization was applied to identify important keywords, and time-dependent overlay visualization was used for research trend analysis. The keywords could be considered as substitutions of scientific ideas, and thus, be used to construct a co-occurrence network. GraphPad 7 was used to analyze the distribution of discipline categories. Microsoft Excel 18 was used to analyze the annual growth trend of current publications. The data obtained, analysis, and verification were all completed by three researchers.

Results

Discipline categories and annual growth trend

Scientific attribute analysis indicated that the discipline categories of YAP1 research mainly focused on oncology (770 publications), followed by cell biology (698 publications), and biochemistry and molecular biology (610 publications) (**Figure 1**). YAP1 research has been of increasing interest (**Figure 2**).

Countries and institutions

In this study, 2,928 publications have co-authors from 75 countries and 2,760 institutions. The top 10 countries and top 15 institutions are shown in **Table 1**. **Figure 3** shows the co-countries and institutions in YAP1 research. Nodes represent countries or institutions, the size of circles represents the number of papers, and the size of nodes corresponds to countries and institutions. As shown in **Figure 3**, China has the highest number of publications, followed by the United States (USA), Japan, Germany, the United Kingdom (UK), South Korea, Canada, France, Italy, and Switzerland. Among the top nine countries with strongest citation bursts, France had the largest burst length (7.95) from 1999 to 2014, suggesting that YAP1 research emerged in France from 1999 to 2014. Israel had the shortest burst length of 3.37, which began in 2008 and ended in 2015 (**Figure 4**). Among the top 15 institutions, 12 were from China and 2 were from the USA. Shanghai Jiao Tong University published the largest number of articles. A centrality value

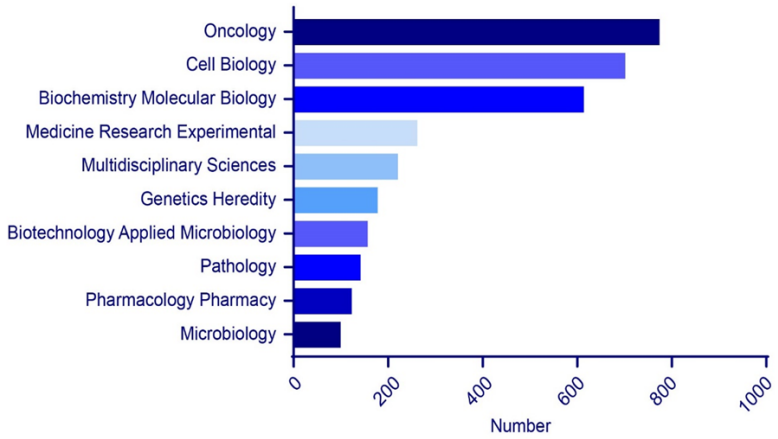

Figure 1. Top 10 discipline categories in YAP1 research.

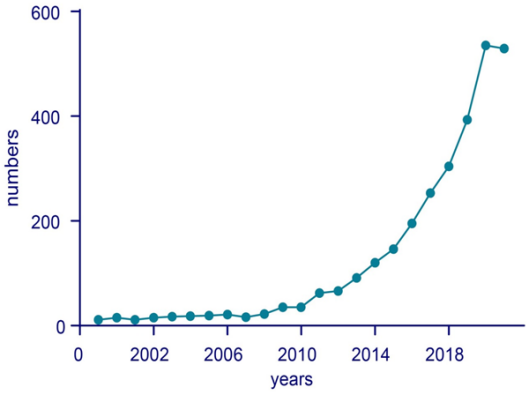

Figure 2. Distribution of publication years.

greater than 0.1 was regarded to be critical and is presented in purple circles. China, the USA, Japan, France, Canada, the UK, and Germany were the most important countries to conduct YAP1 research, with high betweenness centrality (**Figure 5**). Nevertheless, only Harvard University has a high centrality greater than 0.1.

Journals and co-cited journals

CiteSpace was used to conduct citation and co-citation journal analyses. Papers on YAP1 is distributed over a thousand co-cited journals, and eight had over 1000 citations. As shown in **Table 2**, *Cell press* was ranked the first among the co-citations (1864 2.72%), while *Proceedings of the National Academy of Sciences of the United States of America* (*Proc Natl Acad Sci USA*) and *Genes Development* (*Genes Dev*) were ranked second and third, respectively, among the co-citations. Among these 10 journals, nine were at the Q1 Journal Citation Reports (JCR) division with an average Impact Factor (IF) of more than 20. Seven of these journals were from the USA, while the others (3) were from the UK. Furthermore, half of the journals pertain to biology, and 2 were related to medicine. We also found that the largest publishing journal was *J Biol Chem*, followed by *International Journal of Molecular Sciences (Int J Mol Sci)*, *Scientific Reports (Sci Rep)*, and *Oncogene*. Eight out of the ten journals were at the Q1 JCR division, and there were more than five IF in seven journals (**Table 3**).

Authors and co-cited authors

A total of 18,199 authors were involved in the publication of the 2,928 YAP1-related articles. Among the top 10 productive authors in the publication of these articles, nine had more than ten publications. The author Ying Wang had the most publications (n = 24), followed by Randy L. Johnson, and Lei Zhang (n = 16) (**Table 4**). As shown in **Figures 6**, **7**, there were 16 clusters in YAP1 research, and similar color represents strong association with each other, such as Jinjian Kang, Yuan Li, Johnson Randy L, and Xu Yan, which are closely related to each other. In addition, authors (n = 265) who published more than five papers (n > 5) were included in the creation of the density map of the articles.

Co-cited authors refer to authors who were referenced in a series of publications by other authors. Among 59,572 co-cited authors, Bin Zhao (n = 1992) was the highest co-cited author. The author Faxing Yu (n = 820) ranked second, followed by Sirio Dupont (n = 436) and Francesca Zanconato (n = 423). The remaining authors were co-cited within (335-422) as shown in **Table 4**. Density visualization analysis revealed that the authors (n = 82) with co-citations of at least 100 could clearly represent the high frequency authors. As shown in **Figure 8**, Bin Zhao and Faxing Yu were the most co-cited authors.

Table 1. Top 10 countries and 15 institutions involved in Yap1 research

Rank	Country	N%	Centrality	Institution	Counts	Country
1	CHINA	1196 (32.2%)	0.18	Shanghai Jiao Tong Univ	71	CHINA
2	USA	867 (23.3%)	0.4	China Med Univ	68	CHINA
3	JAPAN	241 (6.5%)	0.04	Univ Texas MD Anderson Canc Ctr	67	USA
4	GERMANY	143 (3.2%)	0.18	Nanjing Med Univ	55	CHINA
5	UK	122 (2.9%)	0.13	Sun Yat Sen Univ	51	CHINA
6	SOUTH KOREA	108 (2.5%)	0.01	Zhejiang Univ	50	CHINA
7	CANADA	96 (2.2%)	0.13	Xi An Jiao Tong Univ	48	CHINA
8	FRANCE	80 (1.6%)	0.26	Huazhong Univ Sci & Technol	48	CHINA
9	ITALY	46 (1.2%)	0.04	Harvard Med Sch	43	USA
10	SWITZERLAND	42 (1.1%)	0.04	Nanchang Univ	40	CHINA
11				Harvard Univ	40	USA
12				Fudan Univ	39	CHINA
13				Chinese Acad Sci	39	CHINA
14				Shandong Univ	36	CHINA
15				Sichuan Univ	71	CHINA

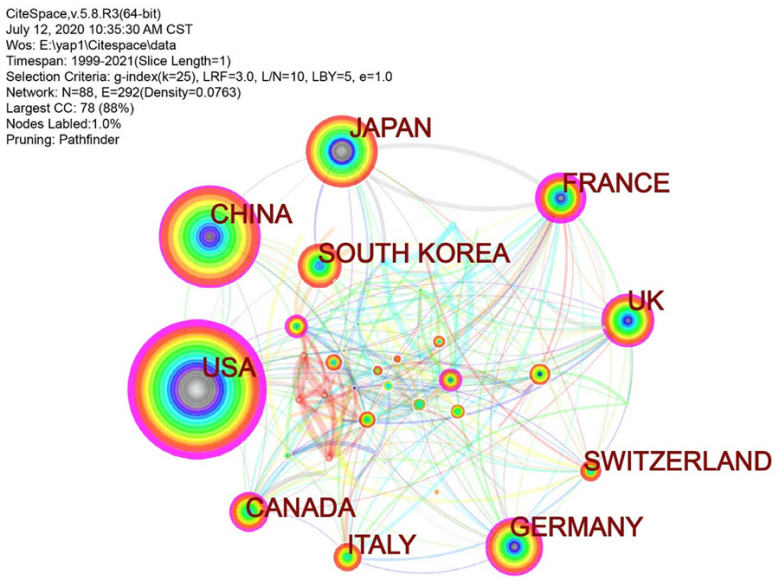

Figure 3. The co-occurrence map of countries. Notes: the size of the node represents the number of articles, and links between countries indicate co-occurrence correlations. Purple circles represent high centrality value (> 0.1).

Keyword co-occurrence, clusters, and evolution

We used VOSviewer to present network of co-occurrence keywords. A total of 5,077 keywords were retrieved, of which 85 co-occurred more than ten times. The network visualization (**Figure 9A**) can facilitate the estimation of hotspots in the research field. As shown in **Figure 5A**, the network was divided into four main clusters. The keywords in each cluster are very synonymous. The color red represents cluster 1, which is the largest with 35 items, including Hippo pathway, prognosis, gastric cancer, Tafazzin (TAZ), cancer stem cells, and (Epithelial-Mesenchymal) EMT. The topic of cluster 1 is the mechanism of YaAP1. Cluster 2 (green) focuses on the clinical application of YAP1 in cancer therapy, and it includes 24 items as follows: therapeutic target, breast cancer, anti-tumor, chemoresistance, drug resistance, cisplatin, etc. Cluster 3 (blue) has 14 items, and is mainly related to biological functions in cancers; the keywords include apoptosis, cell proliferation, cell cycle, osteosarcoma, serine/threonine kinase (AKT), and tumorigenesis Cluster 4, which colored with yellow is mainly related to other functions, and it contains 11 items, including *Saccharomyces cerevisiae (S. cerevisiae)*, oxidative stress, yeast, reactive oxygen species, etc. Color purple to yellow corresponds to the time interval of 2015-2019. In recent years, researchers have mainly focused on the mechanism and translational medicine of YAP1, and this was based on our analysis (**Figure 9B**). As shown in **Figure 10**, *S. cerevisiae* has the highest burst length of

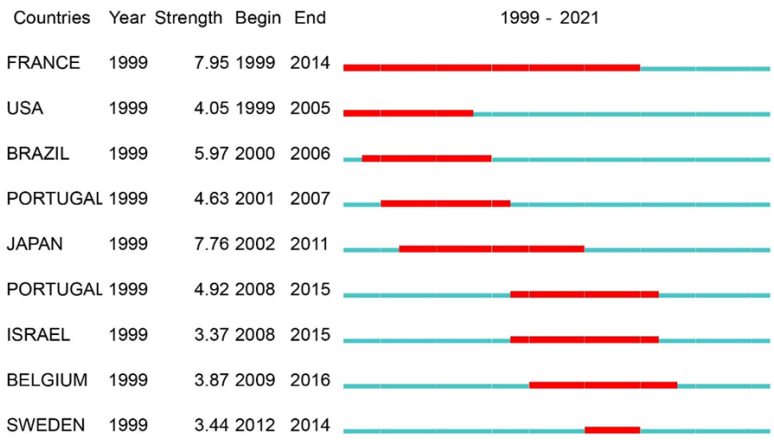

Figure 4. Strongest citation bursts of countries. The length of red bars represent burst time.

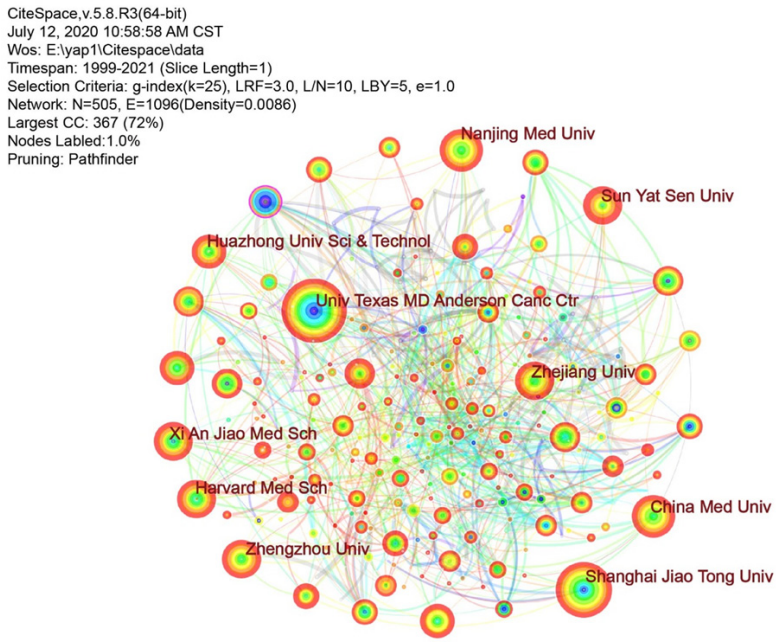

Figure 5. The co-occurrence map of institutions.

51.59. Yeast, as an ideal model system for dissection of eukaryotic DNA repair pathways, is highly conservative in complex organisms. Generally, YAP1 was used for oxidative stress and DNA repair research in *S. cerevisiae* [15, 16]. The implementation of YAP1 in the aforementioned research model started in 1999 and ended in 2014. Meanwhile, many researches focused on YAP1 in oncology. For example, multidrug resistance was also initiated in 1999, which means that the pathophysiological function of YAP1 was burst from the year 1999 to 2010. As shown in **Table 5**, the Hippo pathway, cell proliferation, HCC, TAZ, apoptosis, etc. were high-occurrence words. We classified them into three categories as follows: research models, molecules, and functions. All these key elements represent mainstream themes and frontiers in scientific research. The top 10 occurrence models include hepatocellular carcinoma, S. cerevisiae, pancreatic cancer, colorectal cancer, breast cancer, osteosarcoma, glioma, gastric cancer, lung cancer, and non-small cell lung cancer, indicating that YAP1 research mainly focused on cancer studies. The most occurring molecules are YAP1, Hippo signaling pathway, TAZ, lats, etc. Lastly, the main pathophysiological functions of YAP1 were cell proliferation, apoptosis, oxidative stress, and migration.

Co-cited reference and reference burst

The co-citation analysis of current publications generated 5 co-citation clusters, which were re-arranged by size. **Table 6** provides the details of the 4 clusters. Additionally, the silhouette value of each cluster is greater than 0.9, indicating that the results are reliable and significant. Co-citation cluster analysis revealed that researchers have focused mainly on the function and mechanism of YAP1 in pathological and non-pathological biological models. Combined with highly cited publications, the role of YAP1 in cancer research is at the forefront of the current study.

By analyzing the co-cited references, **Table 7** showed that the top 10 co-cited references were co-cited at least 85 times. The most co-cited reference was a review published in *cell press* by Faxing Yu, with more than 2000 cita-

Table 2. The top 10 co-cited journals of Yap1 research

Rank	Journal	N%	IF (2021)	JCR division	Country	Major disciplines
1	CELL	1864 (2.72%)	41.582	Q1	USA	Biology
2	PNAS	1662 (2.43%)	11.205	Q1	USA	Comprehensive
3	GENE DEV	1500 (2.19%)	11.361	Q1	USA	Biology
4	J BIOL CHEM	1498 (2.19%)	5.157	Q1	USA	Biology
5	NATURE	1410 (2.06%)	49.962	Q1	UK	comprehensive
6	ONCOGENE	1226 (1.79%)	9.867	Q1	UK	Medicine
7	PLOS ONE	1127 (1.65%)	3.24	Q2	USA	Biology
8	CANCER RES	1116 (1.63%)	12.701	Q1	USA	Medicine
9	SCIENCE	958 (1.39%)	47.728	Q1	USA	Comprehensive
10	NAT CELL BIO	902 (1.32%)	28.824	Q1	UK	Biology

Table 3. The top 10 journals of Yap1 research

Rank	Journal	N%	IF (2021)	JCR division	Country	Major disciplines
1	J BIOL CHEM	70 (2.39%)	5.157	Q1	USA	Biology
2	SCI REP	56 (1.91%)	4.379	Q1	UK	Comprehensive
3	INT J MOL SCI	50 (1.71%)	5.923	Q2	USA	Chemistry
4	ONCOGENE	48 (1.64%)	9.867	Q1	UK	Medicine
5	PLOS ONE	47 (1.61%)	3.24	Q2	USA	Biology
6	NAT COMMUN	40 (1.37%)	14.191	Q1	UK	Comprehensive
7	CELL DEATH DIS	38 (1.30%)	8.469	Q1	UK	Biology
8	CANCERS	37 (1.26%)	6.639	Q1	USA	Medicine
9	BBRC	36 (1.23%)	3.575	Q2	USA	Biology
10	PNAS	33 (1.13%)	11.205	Q1	USA	Comprehensive

tions. Following this is a review entitled "YAP/TAZ at the Roots of Cancer" published in *Cancer Cell*. Furthermore, references that are frequently cited in a period of time, also called references with citation bursts, indicate an increased research interest in the field of YAP1. **Figure 11** shows that the strongest burstiness (strength = 33.5) reference was published by Bin Zhao in 2001 [17], followed by an article published in *Curr Biol* by Fernando D. Camargo in 2007, with citation burstiness from 2008 to 2012 [18]. Among the top 20 citation burst articles, we found that four were published by Bin Zhao.

Discussion

General information

According to the current research, 2,928 articles related to YAP1 research were published in 782 journals by 18,199 authors, and they were from 2,760 institutions and 75 countries.

Numerous publications involving YAP1 research have been reported in different categories, especially in oncology (**Figure 1**). The application of YAP1 in cancer therapy may be a hotspot in its research field. However YAP1 research requires an in-depth analysis and summary based on its importance in clinical applications. Annual publications are vital indicators of the development trends in a research field. According to our analysis (**Figure 2**), YAP1 research passed through 3 phases/stages as follows: the "Germination" (1999-2009), involving structural and functional elucidation, and there were 200 articles in these 11 years; "Stable growth" (2010-2013), in which 255 articles were published within 4 years, implying that scientists reached a favorable threshold for burstiness occurrence; and lastly, "Rapid development" stage (2014-2021), involving numerous annual publications (2,473), which was approximately ten times that of the stable growth, indicating that YAP1 research has gained incredible/peak attention by researchers, thus resulting in rapid development. Furthermore, the growth trend of publications seems promising.

YAP1 research is involved in multiple countries and institutions, indicating that its literature

Table 4. Top 10 author and co-cited author

Rank	Author	Count	H-index	Institution	Co-cited author	Co-citation	H-index	Institution
1	Ying Wang	24	54	Fudan university	Bin Zhao	1992	37	Univ Texas MD Anderson cancer center
2	Yan Li	19	60	Chinese Academy of Sciences	Faxing Yu	820	29	University of California San Diego
3	Lei Zhang	16	24	Shanghai Jiao Tong university	Sirio Dupont	436	31	University of Padua
4	Randy L Johnson	16	48	UT MD Anderson cancer center	Francesca Zanconato	423	16	University of Padua
5	Chen xin	18	49	Fudan university	Duojia Pan	422	38	Johns Hopkins University
6	Wei Zhang	18	21	Nanchang university	Jixin Dong	399	26	Johns Hopkins University
7	Akira Suzuki	13	35	Kyushu university	Kieran F Harvey	372	35	Massachusetts General Hospital
8	Hiroshi Nishina	11	48	Tokyo medical & dental university	Yan Wang	355	32	Jinzhou Medical University
9	Sudolmarius	17	52	Yong loo li sch med	Shusuke Kuge	336	20	University of Tokyo
10	Wei Wang	16	39	Shandong university	Varelas Xaralabos	335	30	Boston University

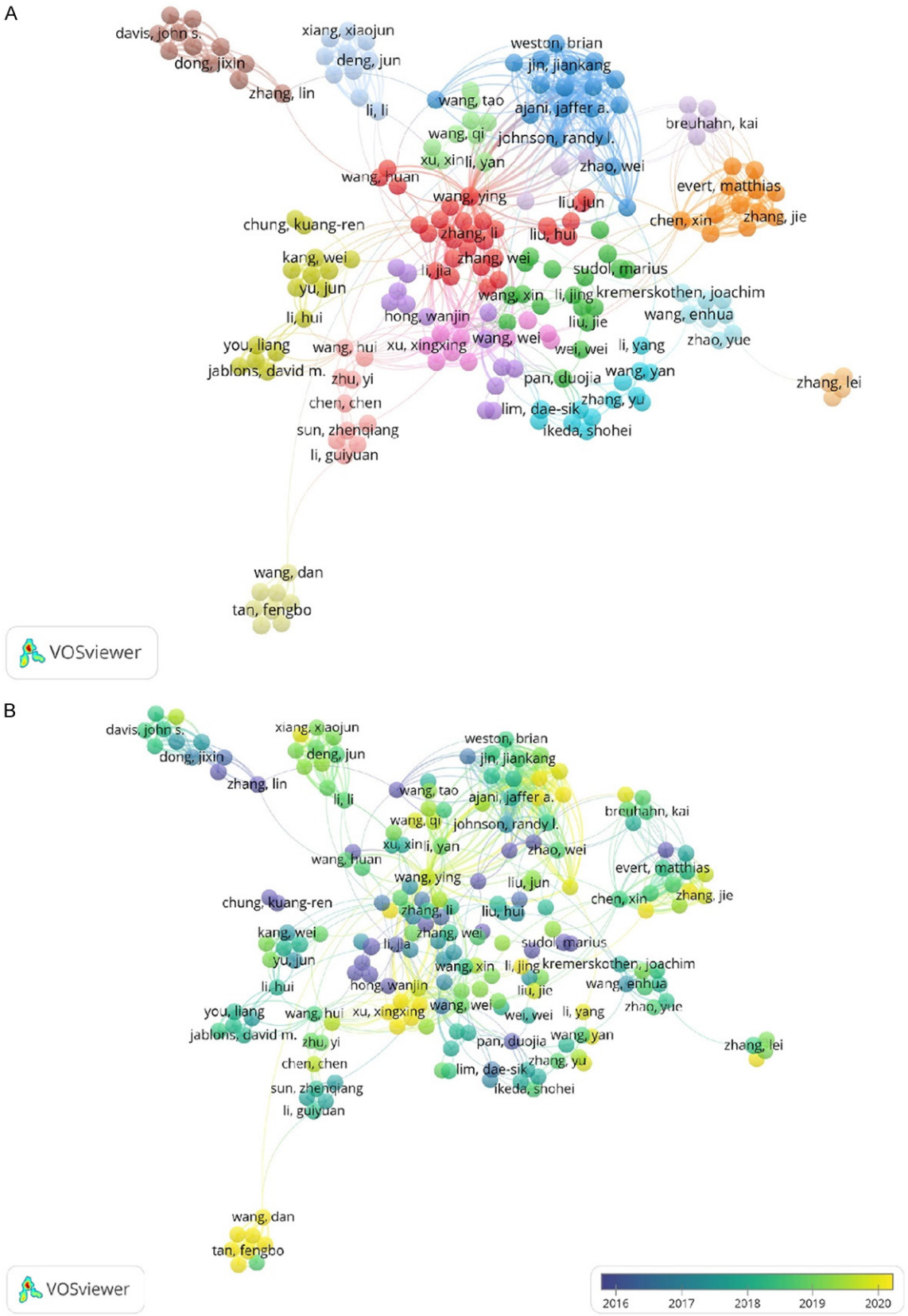

Figure 6. The co-occurrence map of authors in YAP1 research (t > 5). A. Network visualization for authors. B. Overlay visualization for authors.

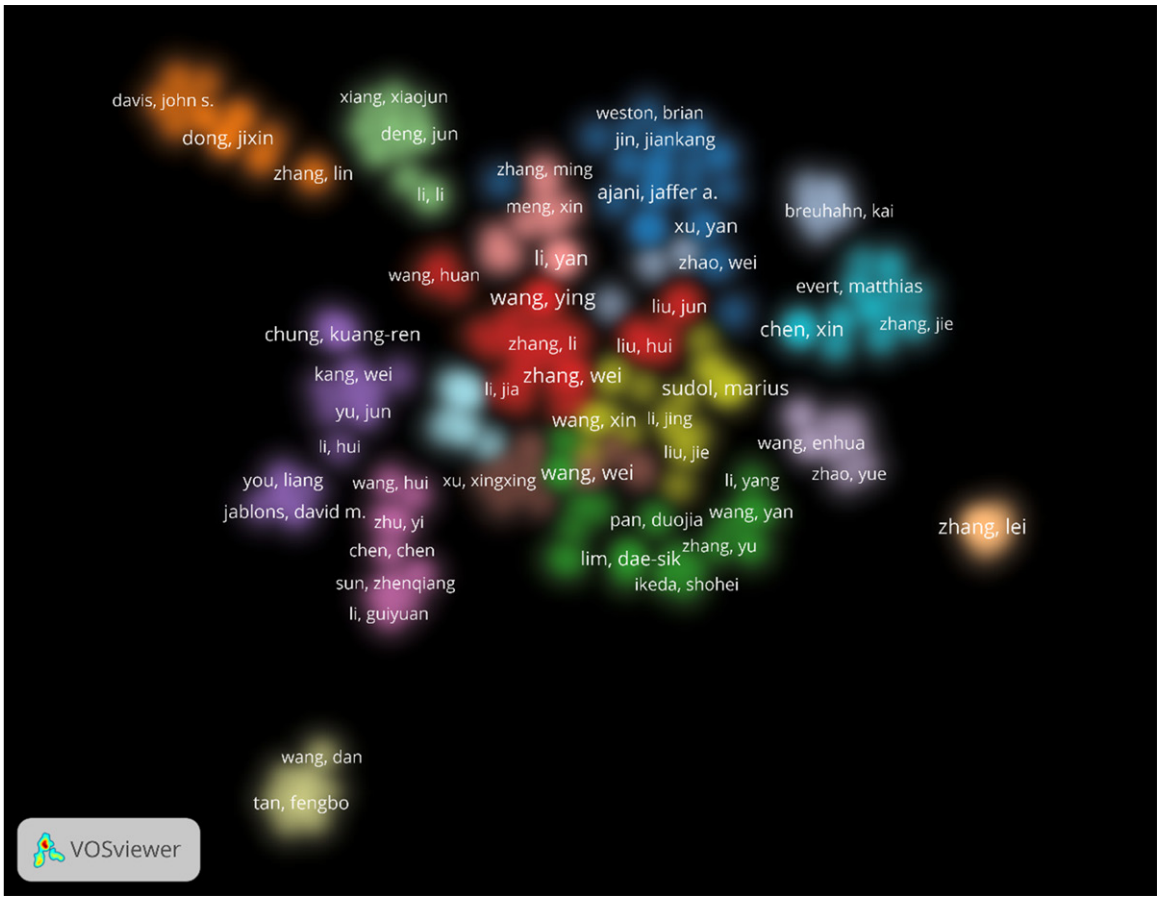

Figure 7. Cluster visualization in YAP1 research, various colors reflect different clusters, the size of the circle and brightness of color are positively correlated with the co-cited citation.

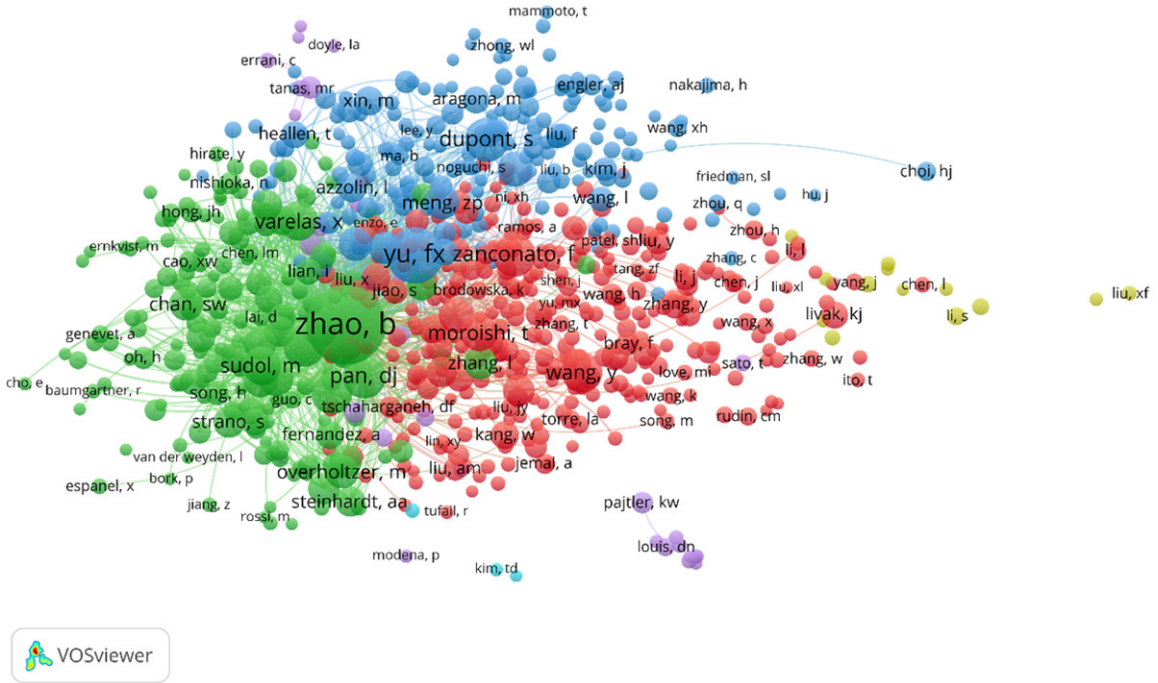

Figure 8. The network map of co-cited authors in YAP1 research (t > 100). Notes: the nodes in the similar color represent the same cluster.

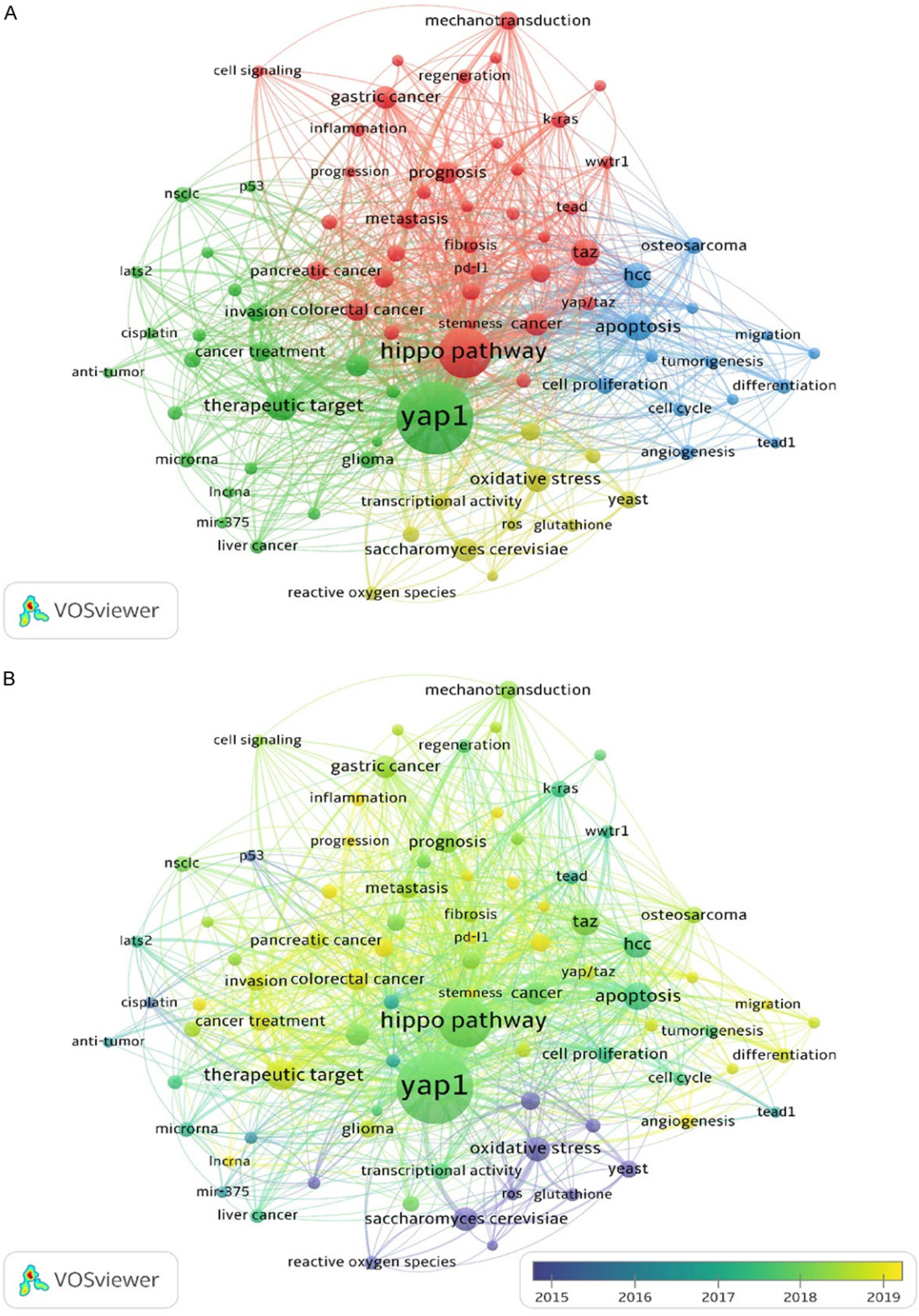

Figure 9. Network plot of keywords in YAP1 research (t > 10). A. Network visualization. Notes: the size of the circles represents the frequency of keywords. B. Overlay visualization. Notes: different colors represent occurrence years, yellow circles represent novel keyword occurrence in recent years, and purple nodes represent keyword occurrence in previous years.

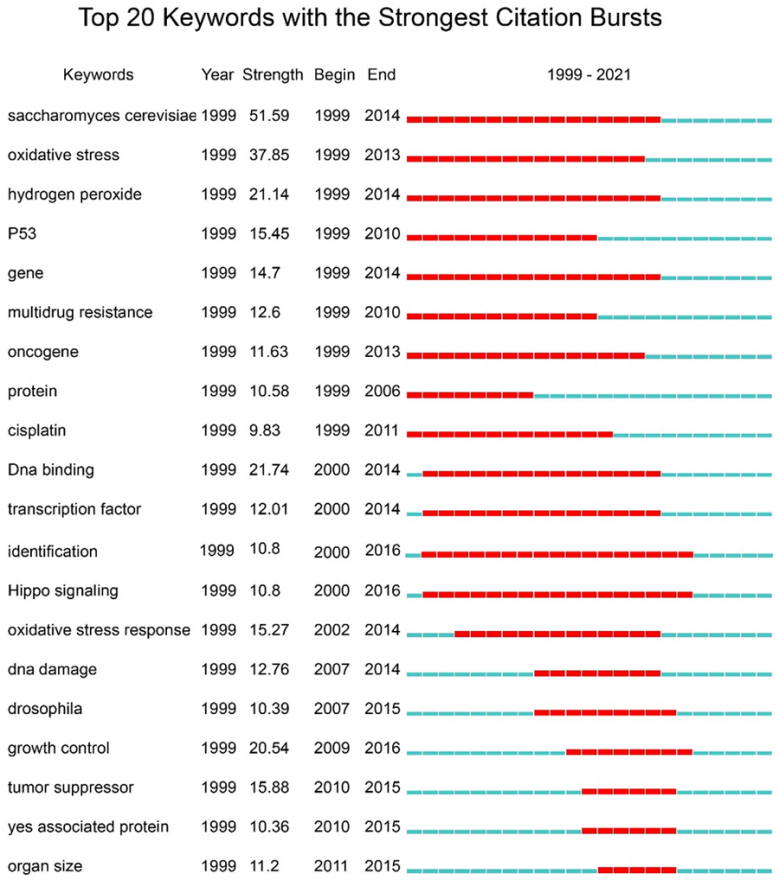

Figure 10. The strongest citation bursts of keywords. Notes: red bars represent the duration of the burst, and the blue bars indicate that the reference had been published.

has gained a global interest. **Table 1** and **Figure 3** show that China, the USA, and Japan are the top 3 productive countries. Notably, China has the largest number of publications, and its centrality value is lesser than that of the USA. Among the top 10 publication countries, 6 (China, USA, France, Canada, UK, and Germany) with higher centrality value (≥ 0.1) were considered to be the important turning points, and may result in revolutionary discoveries (**Figure 4**). Furthermore, France has the largest burst length, indicating that it was the most influential country in YAP1 research. Although China started late, they have emerged as one of the most productive contributors in recent years, suggesting that scientific research may have connections to the economic development and scientific research investment in countries. Notably, among the 15 most active collaborations, 12 institutions were from China (**Table 1**), indicating considerable contributions from China towards YAP1 research.

Journal analysis (**Tables 2** and **3**) showed that *J Bio Chem* is the most productive journal, while *Cell* received the largest number of co-cited references. They officially published articles on YAP1 literature, focusing themes based on biology, medicine, and chemistry, suggesting that YAP1 research pertains to several areas. However, YAP1 research has mainly focused on basic research in recent times, while its clinical application requires further studies for elucidation and implementation. Meanwhile, analysis of the proportion of journals at Q1 JCR indicated that these journals are interested and played important roles in YAP1-related research.

Highlighting the contributors, who published the highest articles or obtained many co-cited papers in a particular research field, can aid scholars who intend to initiate novel research or continue further research, to follow a line of inquiry, by providing effective resources and trends [19]. Notably, Ying Wang published the most articles, while Bin Zhao was the highest co-cited author. However, there was no correlation between the co-occurrence and co-cited authors. Interestingly, aside from being the most co-cited author, Bin Zhao also published 4 references with strong citation bursts (**Figure 11**). Furthermore, the number of authors who conducted YAP1 research has continued to increase in recent years (**Figure 6**), suggesting that the subject still has great potential

Table 5. Most occurrences key disease, molecules, function, and cell types in Yap1 research

Research Model	Occurrences	Total link strength	Molecules	Occurrences	Total link strength	Function	Occurrences	Total link strength
Hepatocellular carcinoma	85	185	Yap1	1035	1471	Cell Proliferation	161	340
Saccharomyces cerevisiae	67	99	Hippo pathway	426	720	Apoptosis	104	212
Gastric cancer	59	128	Taz	92	231	Oxidative stress	76	113
Colorectal cancer	57	118	Transcription Factors	35	56	Prognostic	56	129
Breast cancer	55	99	Lats	26	67	Migration	44	119
Pancreatic cancer	39	79	Wnt	23	66	Metastasis	43	115
Glioma	33	73	Tead	20	57	Invasion	42	1331
Osteosarcoma	31	78	Pdl1	15	39	EMT	38	91
Lung cancer	29	69	Mst1	14	43	Verteporfin	35	100
Non-small cell lung cancer	27	54	P53	12	25	Differentiation	24	56

Table 6. The largest 5 clusters of Yap1 document co-citation, identified by subject headings

Cluster ID	Size	Silhouette	Label (LSI)	Label (LLR)	Label (MI)	Average Year
0	206	0.906	Yes-associated protein	Epithelial-mesenchymal transition (2056.64, 1.0E-4)	Regulatory axis (3.82)	2015
1	183	0.939	Hippo pathway	Cell metastasis (809.18, 1.0E-4)	Lung cancer (0.98)	2015
2	172	0.922	Yes-associated protein	Biomarkers (1839.46, 1.0E-4)	Gastrointestinal cancer (0.89)	2011
3	111	0.901	Yes-associated protein	Hepatocellular carcinoma development (486.48, 1.0E-4)	Rassf1a-mediated regulation (0.3)	2007
4	109	0.866	Yes-associated protein	Brain metastasis (709.9, 1.0E-4)	Adult liver progenitor (0.74)	2017

Table 7. Top 10 co-cited references for Yap1 research

Rank	Type	Title	Journal	Co-citation
1	Review	Hippo Pathway in Organ Size Control, Tissue Homeostasis, and Cancer	CELL	201
2	Review	YAP/TAZ at the Roots of Cancer	CANCER CELL	179
3	Review	The emerging roles of YAP and TAZ in cancer	NAT REV CANCER	146
4	Review	Mechanisms of Hippo pathway regulation	GENE DEV	140
5	Review	The Hippo pathway and human cancer	NAT REV CANCER	135
6	Review	The biology of YAP/TAZ: Hippo signaling and beyond	PHYSIOL REV	105
7	Review	The Hippo pathway: regulators and regulations	GENE DEV	88
8	Review	The two faces of Hippo: targeting the Hippo pathway for regenerative medicine and cancer treatment	NAT REV DRUG DISCOV	87
9	Review	The Hippo signaling pathway in development and cancer	DEV CELL	86
10	Review	Role of YAP/TAZ in mechanotransduction	NATURE	86

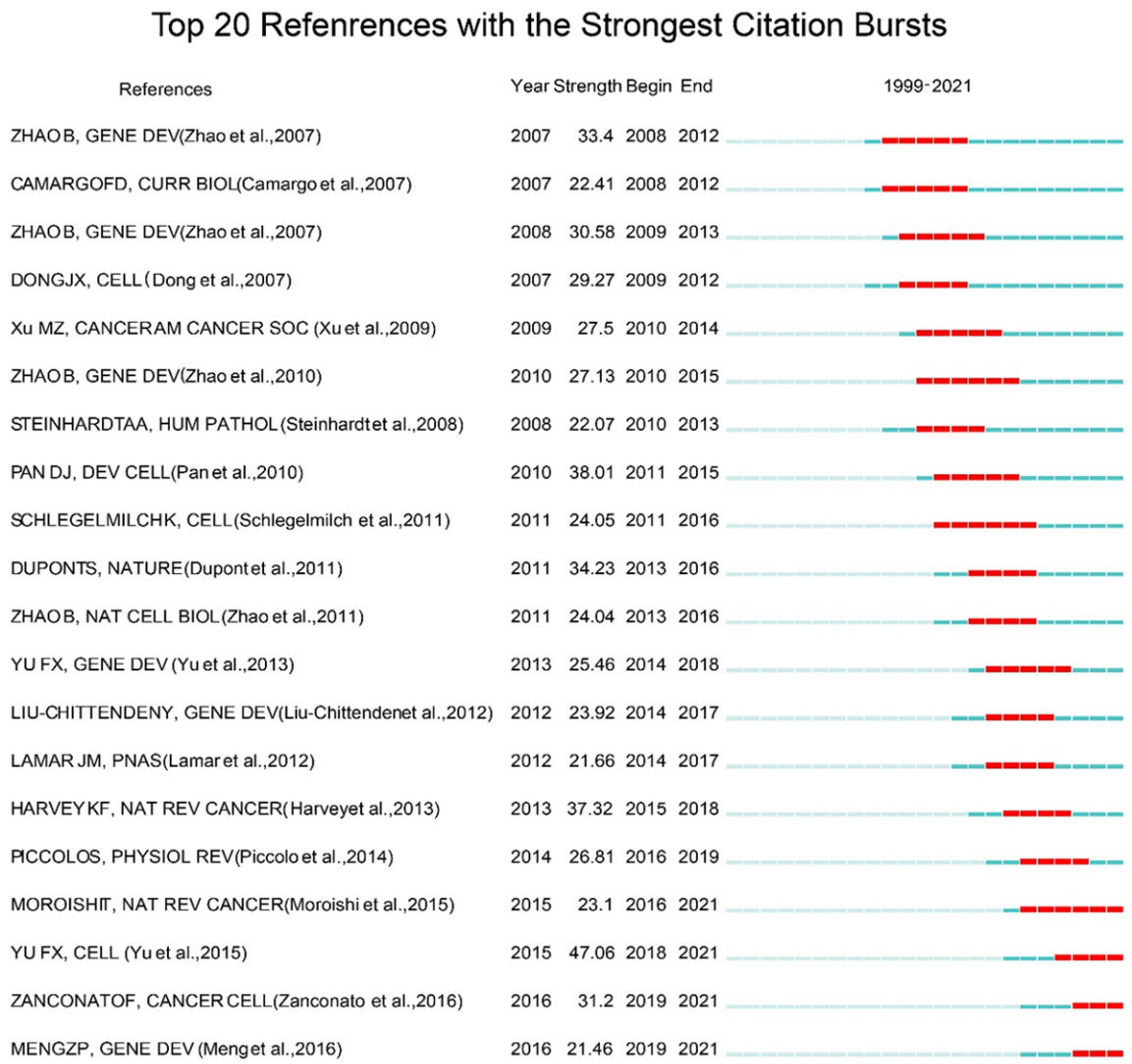

Figure 11. The strongest citation bursts of references. Notes: red bars mean the duration of the burst, and the blue bars indicate that the reference had been published.

research value. Analysis of the authors provided essential information about potential cooperators and research teams [20]. Meanwhile, influential researchers who conducted YAP1 research often cooperated actively within or between institutions.

Illustratively, the most cited author, Bin Zhao, published the most co-cited review entitled "Hippo Pathway in Organ Size Control, Tissue Homeostasis, and Cancer" [1], indicating that this influential author could be potential collaborators for scholars.

Knowledge base

Co-cited references mean publications cited along other articles that are related to a similar research field. The knowledge base is a collection of commonly cited reference articles cited by corresponding research groups [21]. In the present study, the most co-cited references are listed in **Table 7**. *Cell press* published a review in 2015, which was the most co-cited paper (n = 201), making an outstanding contribution in YAP1 research. The review suggests that Hippo could inhibit YAP1 and TAZ transcriptional co-activators to regulate cell growth, stemness, and cell apoptosis, highlighting YAP1 connection with Hippo pathway, and revealing its molecular mechanism towards the development of the body and tumorigenesis. The following year, Francesca Zanconato summarized the functional role of YAP1/TAZ, revealing that its activation promotes the development of cancer [22]. The third study revealed the patho-

logical role of YAP1/TAZ in cancer: Yap1 functions in different ways (acts as an oncogene or as a tumor suppressor gene) according to the cellular context [23]. Meanwhile, numerous proteins and pathways have been linked to YAP1 [24]. The fourth study was published in *Genes Dev.* Journal (2016). In the study, scholars indicated that the upstream signals in Hippo pathway could directly regulate YAP1 localization or transactivation in cancer cells [1, 25]. The fifth co-cited article was published by Harvey in 2013. In the study, researchers proposed emerging therapeutic strategies [4]. The sixth co-cited article was published by Stefano piccolo, et al. in 2014. The article comprehensively described the functional role of YAP1 in body development, tissue homeostasis, and cancer [26]. *Genes Dev* also published the seventh co-cited review by Faxing Yu et al., which summarized the potential implications of the Hippo signaling pathway under physiological and pathological conditions [25]. The eighth co-cited article was published in *Nat Rev Drug Discov* (2014). The article reviewed the functional role of YAP1/TAZ in cancer progression, organ growth, and stemness [27]. The ninth co-cited publication reviewed research progress on the molecular mechanism and physiological function of the Hippo signaling pathway. Nevertheless, the core Hippo kinase cascade leads from mst1 to YAP1 and TAZ, indicating dynamic regulation of development and physiology [28]. The tenth co-cited paper was published by *Nature* in 2011. The review introduced the novel role of YAP1/TAZ in cell function regulation, and suggests that YAP1/TAZ can act as a sensor and mediator of mechanical signals in the cellular microenvironment [29].

Generally, YAP1 and TAZ are known as downstream effector proteins of the Hippo signaling pathway. These proteins have similar functions during tumor progression [30, 31]. Therefore, they are often reported in reviews pertaining the Hippo signaling pathway. The top 10 co-cited references were focused on reviews, and six summarized the role and mechanism of the YAP1/TAZ or Hippo signaling pathway in cancer research. Interestingly, the top 10 papers mainly reviewed the function (cancer cell growth, cell apoptosis, stemness or organ growth, tissue homeostasis.), mechanism (Wnt, K-ras mutation, HER2, G-protein-coupled receptors, msta/2, ECF stiffness, cell contact, attachment), and potential clinical applications (cancer, therapeutic intervention, tissue repair, and regeneration). All these data provided the basic knowledge of YAP1 research.

Hotspot, emerging trend, and knowledge base

Co-occurrence keywords (**Figure 9A**) can reflect the hotspots of the domain of science, and overlay visualization (**Figure 9B**) can provide different colors for nodes through the score or fields based on the research demand. In addition, the score value is obtained according to the average year of keywords for color mapping, which can analyze the evolution of research trends in the field. The high-frequency keywords in YAP1 research (**Figure 8** and **Table 5**) included YAP1, Hippo signaling, cell proliferation, TAZ, apoptosis, among others. In recent years, researchers have mainly focused on cancer research of YAP1 in "Rapid development" (2018-2019), such as chemoresistance, PDL-1, verteporfin, colorectal cancer, and triple-negative breast cancer.

A cluster of keywords provides the internal knowledge structure of an academic field. The largest cluster mainly focused on the mechanism of action of YAP1. The second one focuses on cancer therapy, which may have a potential role in cancer therapeutic intervention. Cluster 3 and 4 pertain to the biological function of YAP1 (**Figure 9**). Moreover, trends in YAP1 research have mainly focused on its functional role under pathological and physiological conditions, including DNA damage, growth control, and ROS (**Figure 10**).

By analyzing the five clusters in YAP1 research (**Table 6**), it can be observed that researchers pay more attention to cancer research, combined with the emerging keywords, therapeutic intervention, and biomarkers of YAP1, which is at the frontier of the current YAP1 research references with strong citation bursts (**Figure 11**), would provide emerging topics in the field [32]. The strongest citation burstiness published in 2007 by Bin Zhao was considered a landmark study. The researchers reported that YAP1 plays a vital role in the Hippo signaling pathway, to regulate cell proliferation through cell contact [17]. Interestingly, Bin Zhao published another original article in the following year, entitled "TEAD mediated YAP-dependent gene induction and growth control". He reported that

TEAD plays key roles in regulating biological function of YAP1 [33]. Bin Zhao summarized the functional role of the Hippo-YAP pathway in tumorigenesis [34]. In 2011, Bin Zhao published another review; he reported the role of the Hippo pathway in body development, and stemness [35]. Among the top 20 strongest citation burstiness references, four were published by Bin Zhao, suggesting that he is an influential author and expert in YAP1 research. Ranking by burstiness strength, the paper with the strongest strength (47.06) was published in *Cell press* by Faxing Yu; his report confirmed that the Hippo signaling pathway is involved in cell proliferation, stemness and apoptosis by inhibiting YAP1 and TAZ transcription co-activators, which aided in the identification of novel therapeutic targets for cancer mitigation [36]. Notably, Bin Zhao is the second author of this review.

YAP1 is closely related to the Hippo signaling pathway, and scholars initially focused on its functional role in cancer. Subsequently, scholars began to identify an in-depth mechanism of YAP1 in cancer pathology, and evaluate its clinical application. Researches on the mechanism of YAP1 will provide new strategies for clinical treatment. Recently, researchers have reported that K-975 was identified as a potent inhibitor of YAP1/TAZ-TEAD, which may become an effective drug candidate for cancer therapy [36]. The development of drug-targeting key molecules for the Hippo pathway, especially the YAP1/TAZ-TEAD complex, has been pursued. However, high selectivity inhibitors require further exploration, and clinical translational applications of specific YAP1 inhibitors are still ongoing.

Limitations

The bibliometric analysis provided some useful information, however, there were also limitations: (1) All data were downloaded only from the WOSCC database, and some studies from other databases were not considered. Nevertheless, WOSCC could provide the sufficient knowledge base, and is also considered as a conventionally applied database for bibliometric analysis. (2) We mainly focused on original articles and reviews; other paper types, such as meeting abstracts, early access, editorial materials, among others, were excluded. Original articles and review articles are the main types of papers, and could present adequate information to researchers [13].

Conclusions

The present article indicates that YAP1 research is in a stage of rapid development and active global cooperation, of which China had published the largest number of papers, and France has a powerful international impact. Active cooperations among countries, institutions and authors promote the progress of YAP1 research. Recently, YAP1 research has mainly focused on its mechanism of action and role in cancer therapy. Clinical research and gene intervention therapy for cancer may also be the emerging trend in YAP1 research.

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Disclosure of conflict of interest

None.

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