Qualitative Study

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Global research status and frontiers on autophagy in hepatocellular carcinoma: a comprehensive bibliometric and visualized analysis

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Background: An extensive body of research has explored the role of autophagy in hepatocellular carcinoma (HCC), revealing its critical involvement in the disease's pathogenesis, progression, and therapeutic targeting. However, there is a discernible deficit in quantitative, analytical studies concerning autophagy in the context of HCC. Accordingly, this investigation endeavored to meticulously assess the evolution of autophagy research, employing bibliometric citation analysis to offer a comprehensive evaluation of the findings in this field.

Methods: The authors conducted a literature search on 2 August 2023, to extract relevant publications spanning from 2013 to 2022, indexed in the Science Citation Index-Expanded (SCIE) of the Web of Science Core Collection (WOSCC). Subsequently, the authors performed a bibliometric assessment of the compiled documents using visualization tools such as CiteSpace and VOSviewer.

Results: The search yielded 734 publications penned by 4699 authors, encompassing contributions from 41 countries and 909 institutions, disseminated across 272 journals, and comprising 26 295 co-cited references from 2667 journals. Notably, China led in publication volume with 264 articles (amounting to 35.9%) and exhibited the most robust collaboration with the United States. The mechanisms underlying autophagy's influence on the emergence and advancement of HCC, as well as the implicated proteins and genes, have garnered significant attention. In recent years, investigations of targeting autophagy and the resistance to sorafenib have surfaced as pivotal themes and emerging frontiers in this domain.

Conclusions: This study rigorously collated and distilled the prevailing research narratives and novel insights on autophagy in HCC. The resultant synthesis provides a substantive foundation for medical professionals and researchers, as well as pivotal implications for future investigative endeavors in this arena.

Keywords: autophagy, bibliometric analysis, hepatocellular carcinoma, sorafenib

Introduction

Primary liver cancer, predominantly hepatocellular carcinoma (HCC), ranked as the sixth most frequently diagnosed cancer and the third leading cause of cancer mortality globally in 2020, with an estimated 906 000 new cases and 830 000 fatalities[1]. HCC constitutes 90% of all liver cancer cases in China[2]. Despite the adoption of multimodal and multidisciplinary treatment strategies, including surgical resection and liver transplantation, HCC patients face a high recurrence rate—up to 70% within 5 years postsurgery, and about 35% post-transplantation[3]. Consequently, understanding HCC pathogenesis and optimizing treatment protocols are pivotal due to the cancer's high incidence and poor prognosis.

HIGHLIGHTS

- This study introduces a pioneering bibliometric analysis within the realm of autophagy as it pertains to hepatocellular carcinoma (HCC).
- A bibliometric analysis of autophagy and HCC literature from 2013 to 2022 reveals a marked surge in the number of publications, with a peak in 2021.
- China emerges as the preeminent nation in the volume of publications, the concentration of researchers, and the number of institutions dedicated to studying the interplay between autophagy and HCC, demonstrating a particularly close collaborative relationship with the United States.
- Current research has increasingly focused on elucidating the mechanisms and associated proteins of autophagy, with a special emphasis on its role in targeting autophagy and sorafenib resistance, positioning these areas as the current hot topics and frontiers in the discipline.

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Recent research has elucidated a significant link between autophagy—a cellular degradation pathway that maintains cellular equilibrium and supports energy production—and various liver diseases, including nonalcoholic fatty liver disease[4,5], hepatic fibrosis[6], drug-induced liver injury[7], and liver tumors[8,9]. Given its crucial role in cellular survival, differentiation, development, and homeostasis, most studies on autophagy, specifically macroautophagy, have provided valuable insights into its dual nature in HCC progression[10–13]. Autophagy facilitates tumor suppression before cellular transformation by preserving genomic stability and mitigating tumorigenic inflammation. Conversely, post-transformation, autophagy aids tumor cell survival by satisfying heightened metabolic demands[10,12–14]. Additionally, faulty autophagy, indicated by deletions of essential autophagic components such as Beclin-1, Atg5, or Atg7 in murine models, has been shown to foster spontaneous liver tumor development[15–17]. However, established tumors can exploit autophagy under stress conditions like hypoxia or nutrient scarcity to progress, and evidence suggests that autophagy may also enhance HCC cell invasion via epithelial-mesenchymal transition (EMT) activation[18–21].

The application of bibliometric analysis in oncology research has surged, leveraging statistical techniques and visualization tools to reveal pivotal studies and evolutionary trends[22]. The insights gained from such analyses, particularly through intuitive visual representations, have offered novel perspectives in cancer treatment[22–24]. Despite these advancements[25], a visual bibliometric analysis addressing autophagy in the context of HCC remains unreported. Addressing this gap, our study conducts a comprehensive, multidirectional quantitative assessment to elucidate the landscape of autophagy in HCC research. The goal is to furnish clinicians and researchers with a synthesized overview of current developments and potential future trajectories for autophagy in HCC treatment and understanding.

Materials and methods

Literature search and screening

In this study, we utilized bibliometric methodologies to conduct a comprehensive analysis of the literature on autophagy in HCC. Our search was conducted through the Web of Science Core Collection (WoSCC), an extensive database that includes primary citation sources, peer-reviewed journals, and conference proceedings. On 2 August 2023, we retrieved articles published between 2013 and 2022 indexed within the Science Citation Index Expanded (SCIE) of the WoSCC. We applied the search terms 'primary hepatic cancer', 'hepatocellular carcinoma', 'primary liver cancer', 'primary liver carcinoma', and 'autophagy'. The detailed search strategy is outlined in Supplemental File S1 (Supplemental Digital Content 1, http://links.lww.com/JS9/B971). Inclusion criteria were limited to English-language, peer-reviewed 'article' and 'review' to ensure the relevance and quality of the data. We exported the literature records with the option 'Full record and cited references' and formatted the output in plain text. Two independent reviewers (J.Z. and K.S.) screened the initial dataset, removed duplicates and irrelevant studies, and in cases of disagreement, a third reviewer (T.H.) was consulted to resolve discrepancies. This study aligns with the Consolidated Criteria for Reporting Qualitative Research (COREQ)[26] (Supplemental Digital Content 2, http://links.lww.com/JS9/B972).

Statistical analysis and visualization

Publication counts by year were tabulated and analyzed using Excel 2019. The trend of annual publications on autophagy in HCC was graphically represented using GraphPad Prism (version 8.0.2). Institutional affiliations, co-cited references, and keyword trends were evaluated using CiteSpace (version 6.1 R6), with a time-slice setting of 1 year and a top N of 50 and a g-index factor k of 15. Nodes within the visual network maps were color-coded to indicate chronology, with warmer colors representing more recent contributions. Analysis of authors, co-cited authors, journals, and co-cited journals was performed with VOSviewer (version 1.6.18). Collaborative networks were visualized using SCImago Graphica Beta (version 1.0.18), where node size indicated frequency and citation count. The study's flowchart is depicted in Figure 1.

Results

The investigation encompassed contributions from 4699 authors across 909 institutions in 41 countries, culminating in 734 publications, which included 651 original research articles and 83 reviews. These works were disseminated across 272 journals and cited a total of 26 295 references from 2667 distinct journals.

Trends in publications

The number of publications per annum is indicative of trends within the field. An upward trajectory in annual publication volume was observed (Fig. 2). The predictive equation for cumulative publication count (Y) as a function of publication year (x) is $Y = 3E\text{-}291e0.3343x$, which forecasts the annual publication count with an R-squared value of 95% ($R^2 = 0.9528$). In particular, the annual average output was ~73 papers, with 2021 registering the highest number of publications ($n = 118$).

Distribution of countries and institutions

Figure 3 A illustrates the collaborative network among the countries that have published manuscripts on autophagy in HCC, with China at the forefront of international cooperation, especially with the United States. Among the 41 contributing countries (Fig. 3B), China leads with 264 publications, comprising 35.9% of the total output, a proportion significantly higher than any other country, followed by the United States ($n = 80$), the Republic of Korea ($n = 65$), and Japan ($n = 44$).

In the institutional analysis, 1088 entities worldwide have contributed to the field of autophagy in HCC. Figure 4 delineates the most prolific organizations in terms of publication volume. Remarkably, the top 10 institutions with the highest number of publications are located in China, with Zhejiang University ($n = 36$), Fudan University ($n = 35$), and Sun Yat-Sen University ($n = 27$) leading the count, garnering 1116, 1045, and 1140 total citations, respectively (Table 1). Notably, Nanjing University is distinguished by having the highest average number of total citations per publication (TCs, $n = 56.4$).

Analysis of authors and co-cited authors

The authorship landscape, comprising over 4000 contributors, is mapped out in Figure 5A, highlighting key authors and their collaborative networks. Echoing the geographical distribution of publications, the top 10 most prolific authors are predominantly

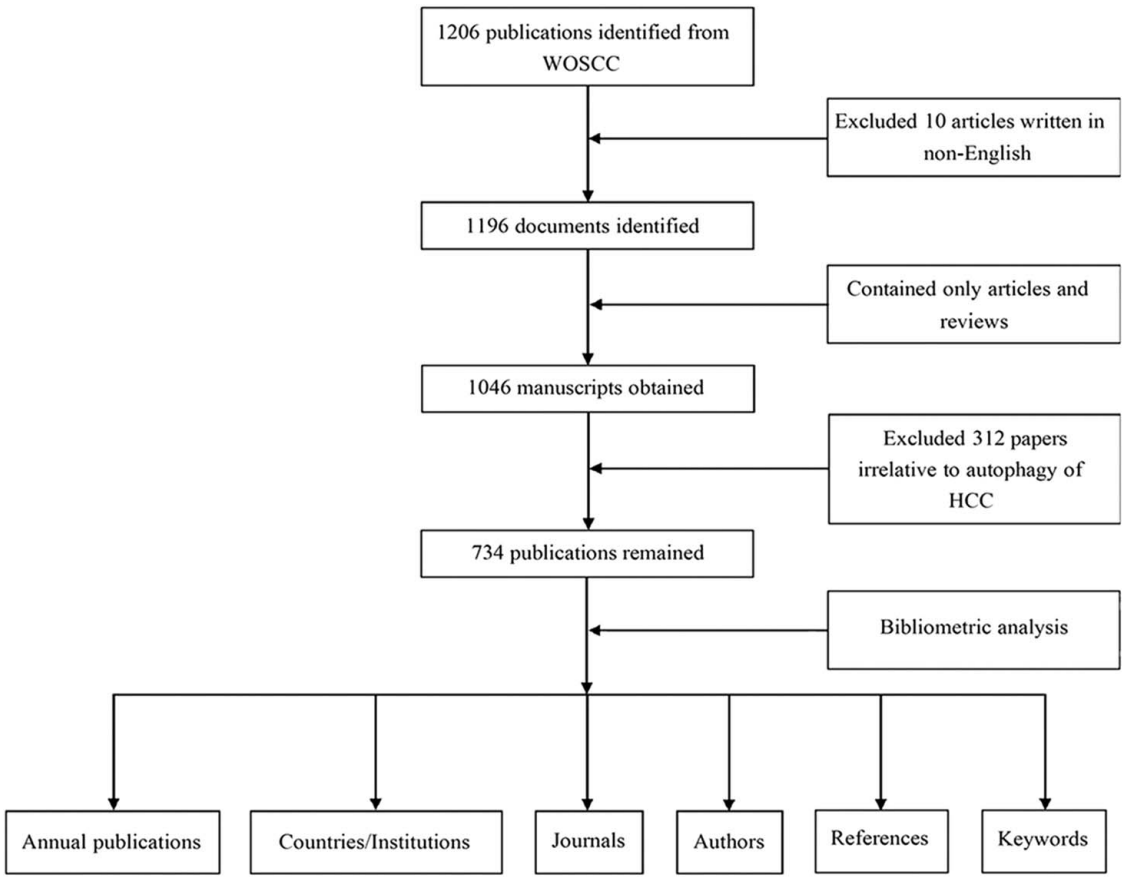

Figure 1. A flowchart of the research process to retrieve documents on autophagy and HCC from the WosCC database.

based in China (Table 2). The leading authors by publication count are Zhou J, Fan J, and Chen W, each with nine manuscripts to their credit. In terms of co-citation, 18 279 authors have been co-cited at least once, with six authors achieving a minimum of 100 co-citations. Notably, only one Chinese scholar features among the top 10 co-cited authors, whereas five are from the United States (Table 2). Figure 5B visualizes this data, showing Mizushima N from Japan as the most co-cited scholar with a total of 293 citations, followed closely by Llovet JM and Levine B from the USA, with 201 and 165 citations, respectively. Additionally, Mizushima N is recognized for robust collaborations with researchers such as Takamura A, White E, and Wang Y.

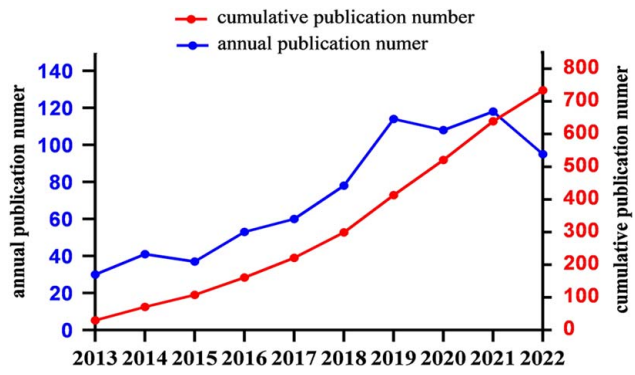

Figure 2. Number of publications by year (Y = 3E-291e0.3343x and R2 = 0.9528, where Y is the cumulative publicaton number and x is the published year).

Analysis of active journals and co-cited journals

Our study found that 272 peer-reviewed journals published 734 documents on HCC autophagy between 2013 and 2022. Table 3 lists the journals with the most contributions to autophagy and HCC research. Notably, *Cell Death & Disease* led with 27 publications. However, the journal *Autophagy* demonstrated superior citation metrics, with the highest total citations (TCs, $n = 1599$), the highest average TCs per document ($n = 72.7$), and the most impressive impact factor (IF2022: 13.3, Q1). Furthermore, ~80% of the top 10 journals are ranked as Q1 or Q2 in the Journal Citation Reports (JCR). Figure 6A highlights emerging journals, including Frontiers in Oncology (IF: 4.7, Q2), Cancers (IF: 5.2, Q2), and International Journal of Biological Sciences (IF: 9.2, Q2).

Among 2667 co-cited journals, 12 received over 500 citations each. As depicted in Table 4 and Figure 6B, aside from *Oncotarget*, the top 10 co-cited journals belong to Q1 or Q2 categories, featuring prestigious publications such as *Nature* (IF: 60.9, Q1) and *Cell* (IF: 64.5, Q1). The journal *Autophagy* ranks as the most co-cited, with 1467 citations, followed by *Hepatology* (IF: 13.5, Q1) and *Cell* (IF: 64.5, Q1).

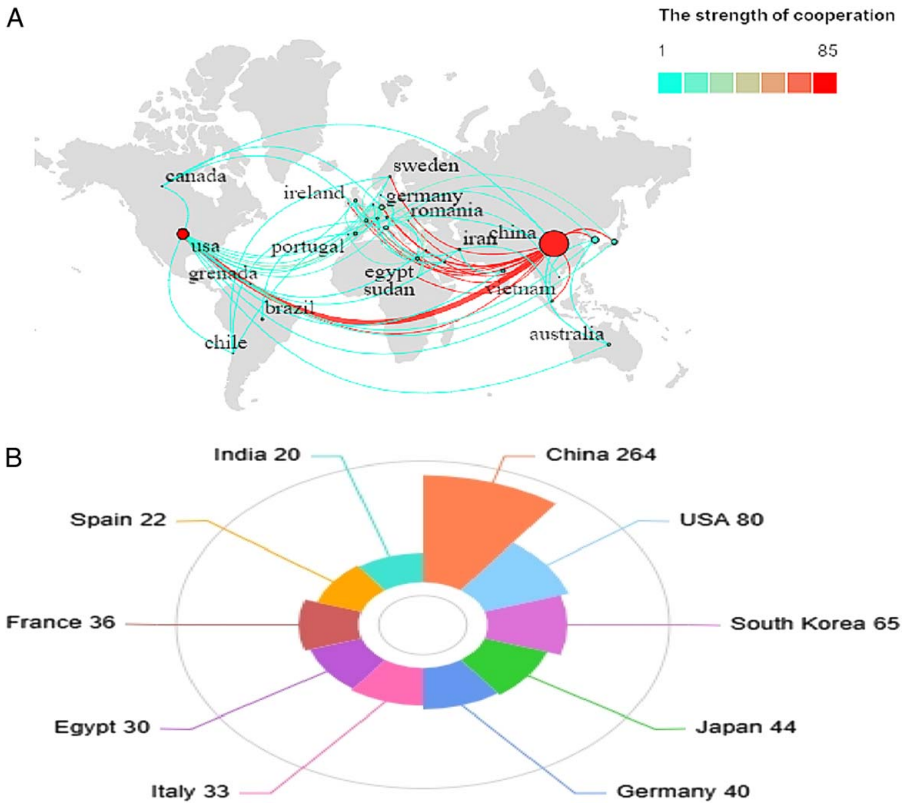

Figure 3. A. The network map of countries cooperation (the size of the node represents the number of publications, and the color of the line shows the strength of cooperation). B. Top 10 countries in terms of number of publications.

Dual map overlays were used to reflect scientific contributions, illustrating citation networks and validating current research foci. These overlays showcase the citation trajectory, knowledge flow, and manuscript distribution related to autophagy. Journal clustering was performed using the Blondel algorithm. As depicted in Figure 7, the dual map overlay comprises two halves: the left side indicates the distribution of journals containing citing literature in the field of autophagy, and the right side shows the distribution of journals where cited literature appears. The central ellipse of Figure 7 denotes specific journal subject areas, with the left ellipse's axes representing author counts and publication numbers, and the right ellipse's axes representing counts of cited authors and journals. The interconnecting links visualize citation relationships. The yellow main path indicates frequent citations from molecular/biology/immunology journals to those in the medicine/medical/genetics domain.

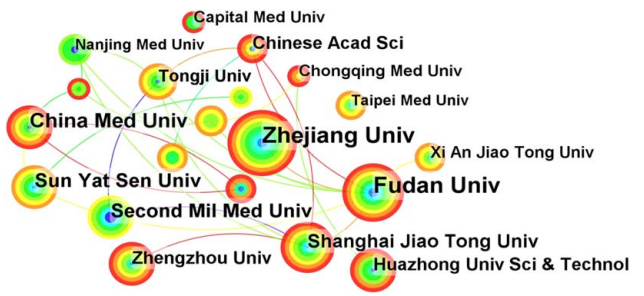

Figure 4. The bibliometric analysis of active institutions in the autophagy and HCC research (the lines represent cooperation relationships, and the colors in the nodes).

Contribution of documents and co-cited references

In our analysis, the top 10 most cited documents included nine articles and one review, as listed in Table 5. The most cited paper was 'The long noncoding RNA lncTCF7 promotes self-renewal of human liver cancer stem cells through activation of Wnt signaling' by Wang Y *et al*.[27] from China, published in *Cell Stem*

Table 1

The top 10 institutions contributed to publications in the autophagy and HCC research.

Rank	Institution	Country	Counts	TCs	Average TCs
1	Zhejiang University	China	36	1116	31.0
2	Fudan University	China	35	1045	29.8
3	Sun Yat-Sen University	China	27	1140	42.2
4	China Medical University	China	25	845	33.8
5	Second Military Medical University	China	23	870	37.8
6	Shanghai Jiaotong University	China	21	920	43.8
7	Tongji University	China	16	442	27.6
8	Zhengzhou University	China	16	278	17.4
9	Nanjing University	China	15	846	56.4
10	Huazhong University of Science and Technology	China	15	789	52.6

Average TCs: the ratio of TCs to publication counts.
TCs, total citations.

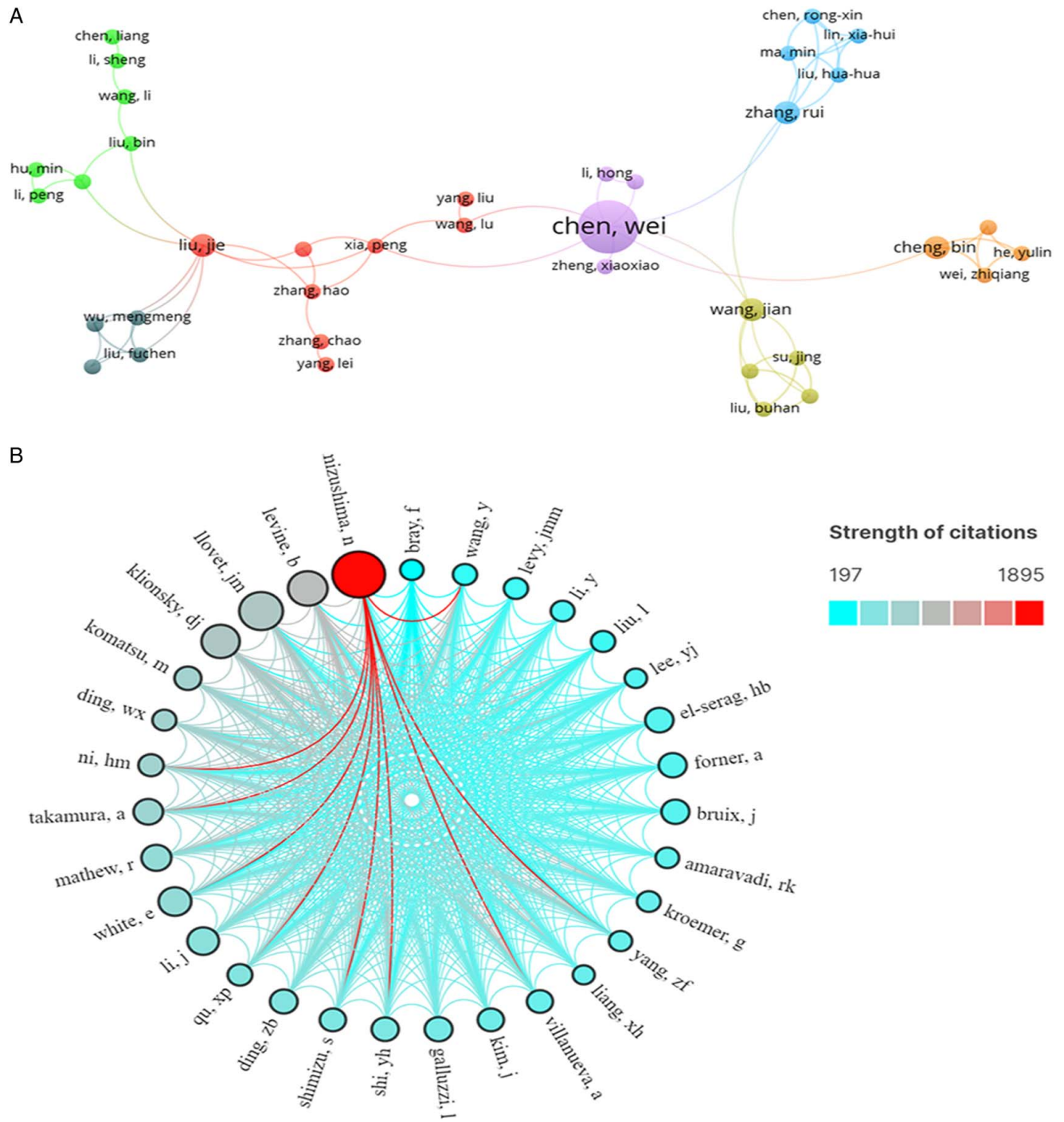

Figure 5. The knowledge map of active authors and co-cited authors in the field of HCC and autophagy research. The node size represents the frequency of authors. A. Active authors. B. Active co-cited authors (the color of the line shows the strength of citations).

Cell in 2015, with 460 citations. Three influential manuscripts were from the journal *Autophagy*, including a 2016 article with 213 citations and two publications from 2013, one being a review and the other an article, with 353 and 190 citations, respectively.

Furthermore, we aggregated the top 10 co-cited references in autophagy and HCC research from among 26 295 references. Notably, four of these references originate from Japan, with the remaining six distributed between China, the United States, and Spain. Table 6 shows that the most co-cited articles in this field are by Takamura A *et al.*[15] and Llovet JM *et al.*[28], with 91 and 75 citations, respectively. Moreover, using CiteSpace, we characterized the relationship between co-cited references, presenting a timezone view that identifies highly co-cited works for each year from 2013 to 2022 (Fig. 8A). Clusters are ordered by size, with a smaller ordinal value indicating a larger cluster. As illustrated in

Table 2

The top 10 authors and co-cited authors in the autophagy and HCC research.

Rank	Author	Country	Documents	Co-cited author	Country	TCs
1	Zhou Jian[2]	China	9	Mizushima N	Japan	293
2	Fan Jia	China	9	Llovet JM	USA	201
3	Chen Wei	China	9	Levine B	USA	165
4	Yang Liang	China	8	Klionsky DJ	USA	154
5	Wang Yu[27]	China	7	White E	USA	113
6	Shi Yinghong	China	7	Li Jun	China	105
7	Li Jun[21]	China	7	Mathew R	Singapore	94
8	Li Hangyu	China	7	Takamura A	Japan	91
9	Ding Zhenbin	China	7	El-serag HB	USA	84
10	Wang Tao	China	6	Bruix J	Spain	82

TCs, total citations.

Figure 8B, cluster '#0 hepatocellular carcinoma' is the largest in this study. Additionally, '#2 sorafenib inhibit' has emerged as a prominent research topic in recent years.

Analysis of keywords and burst keywords

Keywords are indicative of a document's core concepts. Our analysis encompassed 2585 keywords extracted from 734 manuscripts, with 18 keywords recurring over 50 times. A visual map (Fig. 9A) was constructed to illustrate the most frequently mentioned keywords, shedding light on the research focus areas within autophagy and HCC. The network map, segregated into five color-coded clusters, reveals strong thematic homogeneity within each cluster. 'Autophagy' surfaced as the most prevalent keyword, followed closely by 'hepatocellular carcinoma' and 'apoptosis', each appearing over 200 times. Other keywords such as 'inhibition', 'pathway', 'mechanism', and 'sorafenib' also held considerable prominence.

The clusters are delineated as follows: Cluster 1 (red) integrates terms like 'autophagy', 'apoptosis', and 'endoplasmic reticulum stress'; Cluster 2 (green) encompasses 'hepatocellular carcinoma', 'survival', and 'proliferation'; Cluster 3 (blue) includes 'sorafenib', 'chemotherapy', and 'epithelial-mesenchymal transition'; Cluster 4 (yellow) contains 'signaling pathway', 'target', 'ampk', and 'akt'; and Cluster 5 (purple) groups 'p53', 'gene', and 'protein'. Keywords with significant burst values denote intensively cited concepts within specific time frames, often signaling emergent research directions. As reflected in Figure 9B, 'autophagy-related gene' has recently emerged as a pivotal research topic.

Table 3

The top 10 journals that contributed to publications in the field of autophagy and HCC.

Rank	Journal	Counts	TCs	Average TCs	IF2022	JCR area
1	Cell Death and Disease	27	1186	43.9	9.0	Q1
2	Autophagy	22	1599	72.7	13.3	Q1
3	Oncotarget	21	886	42.2	0	0
4	Cancer Letters	19	810	42.6	9.7	Q1
5	Biochemical and Biophysical Research Communications	19	518	27.3	3.1	Q2
6	Oncology Reports	19	456	24.0	4.2	Q2
7	Frontiers in Oncology	17	140	8.2	4.7	Q2
8	Scientific Reports	15	454	30.3	4.6	Q2
9	Oncology Letters	14	223	15.9	2.9	Q3
10	Plos One	14	621	44.4	3.7	Q2

JCR, journal citation reports; TCs, total citations.

Discussion

Autophagy plays a crucial role in the onset and progression of HCC and is increasingly recognized as a vital therapeutic target[10,11]. This study's analysis of publication trends, geographic distribution, collaborative networks, and research hotspots aims to deepen our understanding of autophagy's role in HCC and catalyze the development of innovative treatment strategies for this malignancy.

Countries/institutions and their cooperation

Our findings suggest a notable growth in autophagy research within HCC over the last decade, with a marked surge from 2018 to 2019 and a peak in 2021. This uptrend highlights the escalating scientific interest in autophagy's relevance to HCC. Publications from the top 10 countries spanned across Asia, Europe, the Americas, and Africa, contributing 53.5, 17.8, 10.9, and 4.1% of the total, respectively. Although only three of these countries are considered developing, they accounted for 42.7% of the literature, with China notably leading in publication volume, echoing the findings of Fan *et al*.[29] Chinese institutions notably dominate the top 10 list, reflecting the pivotal role of Chinese researchers in this field. This phenomenon may be attributed to the higher HCC prevalence in Asia compared to Europe and the increased emphasis on cancer research in developing nations[1,30]. Zhejiang University emerged as the most prolific institution, maintaining extensive collaboration with peers such as Fudan University and Shanghai Jiao Tong University, potentially facilitated by geographical proximity. While China and the United States demonstrate robust research collaboration, the engagement with other global partners appears relatively limited. China, having collaborated with over 10 countries, occupies a central position in the cooperative network, but alliances with European and American nations offer potential for further enhancement.

Citation information

High citation counts are typically associated with high-quality research that exerts a significant influence on innovation and discovery within a field; generally, the more citations a study receives, the greater its impact[31]. Our analysis revealed that the top 10 authors by publication volume were all from China, aligning with the country's prominent role in the national publication statistics. However, despite this high output, only one Chinese scholar appeared among the top 10 co-cited authors, with half of the top co-cited authors hailing from the United States. This discrepancy suggests that Chinese scientific publications may benefit from further enhancements in quality to achieve wider global influence.

Professor Mizushima Noboru from the University of Tokyo, Japan, stands out as the most frequently co-cited author, credited with defining molecular aspects of autophagy and related processes[32], as well as advancing the field from cell biology to physiology and disease applications[33]. Additionally, Professor Klionsky DJ from the University of Michigan, USA, as the fourth

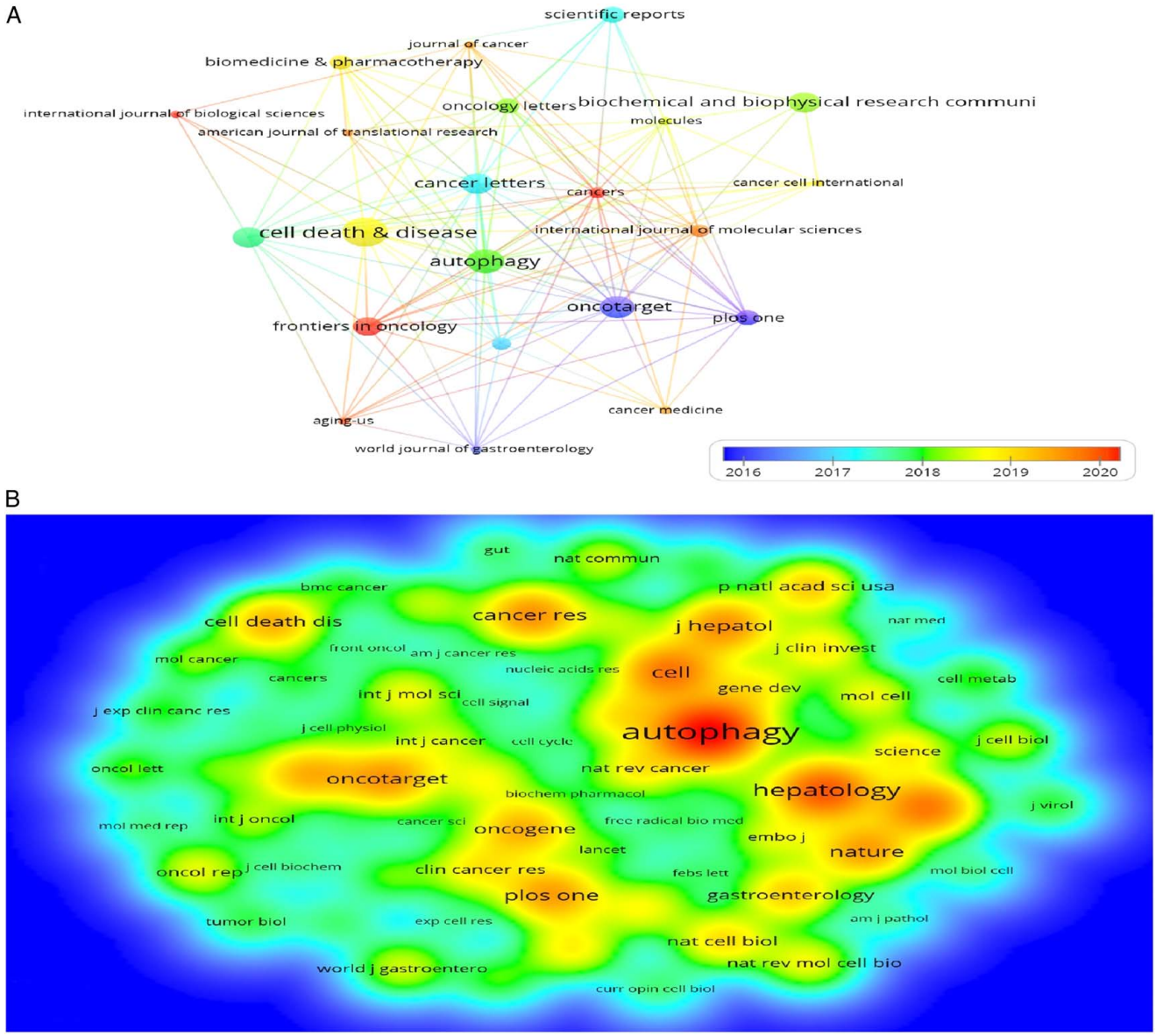

Figure 6. The bibliometric analysis of active journals and co-cited journals in the HCC and autophagy research. A. Active journals. B. Active co-cited journals. The colors in the nodesrepresent the years.

Table 4

The top 10 co-cited journals associated with autophagy of HCC.

Rank	Journal	TCs	IF2022	JCR area
1	Autophagy	1467	13.3	Q1
2	Hepatology	970	13.5	Q1
3	Cell	798	64.5	Q1
4	Journal of Biological Chemistry	793	4.8	Q2
5	Cancer Research	688	11.2	Q1
6	Journal of Hepatology	682	25.7	Q1
7	Oncotarget	628	0	0
8	Nature	623	60.9	Q1
9	Plos One	623	3.7	Q2
10	Cell Death & Disease	560	9.0	Q1

TCs, total citations.

most co-cited author (Table 2), has made pivotal contributions to the foundational understanding of autophagy. Klionsky has been instrumental in formulating guidelines for monitoring autophagy[34,35] and has participated in influential research delineating the morphology, molecular mechanisms, and regulation of mammalian autophagy[36]. These works have not only deepened our understanding of autophagy but also facilitated the development of novel therapeutic interventions for diseases where autophagy dysregulation is a factor.

The IF of the top 10 journals and co-cited journals indicates varying levels of influence. Among the top 10 journals, 66.7% boast an IF greater than 9, with over 80% ranked as Q2 or higher in the JCR. This data underscores the robust interest and significant role that high-quality, high-impact journals play in advancing research on autophagy and HCC.

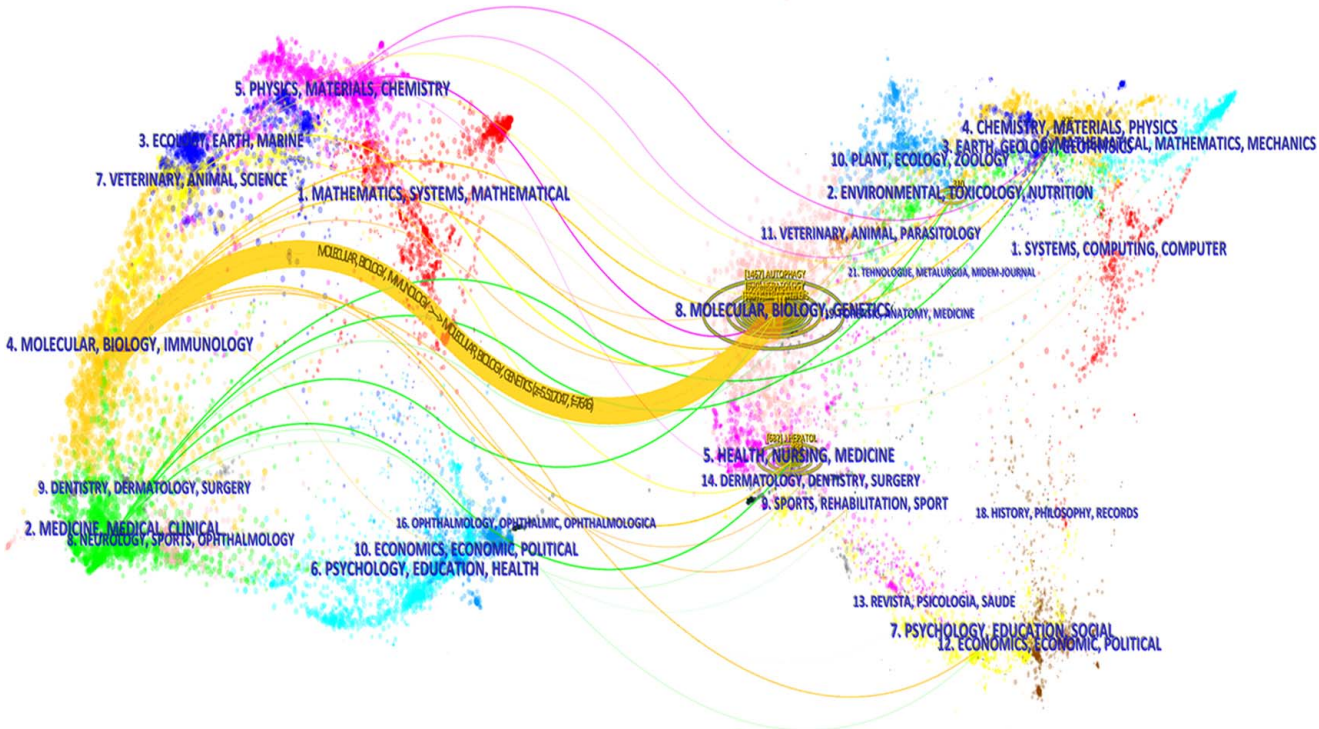

Figure 7. The dual map overlay of journals in the field of autophagy in HCC (left, citing journals; right, cited journals).

Cell Death & Disease has published the most articles, yet it has the lowest citation count among the top 10 co-cited journals. In contrast, Autophagy not only received the highest number of citations but also maintains a high IF. This can be attributed to its focus as a specialized journal within the autophagy domain, consistently featuring relevant publications that garner increasing citations annually. Notably, *Frontiers in Oncology* and *Cancers*, both from the prolific Swiss publishers Frontiers and MDPI respectively, have emerged as significant journals over the past three years. Their rise suggests a growing preference among researchers to submit their work to open-access journals that offer expedited publication timelines from acceptance to online availability. This trend reflects a shifting publishing landscape where open access and rapid dissemination are increasingly valued by the scientific community.

The top 10 cited manuscripts, presented in Table 5, predominantly consist of fundamental experimental research articles focusing on autophagy-related signaling pathways, with one exception being a review. The majority, eight out of ten, of these highly cited papers originate from China, with the other two being

Table 5

The top 10 cited manuscripts in the field of autophagy and HCC.

Rank	Title	Journal	Type	Publication year	TCs
1	The long noncoding RNA lncTCF7 promotes self-renewal of human liver cancer stem cells through activation of Wnt signaling	Cell stem cell	Article	2015	460
2	Functions of autophagy in normal and diseased liver	Autophagy	Review	2013	353
3	LncRNA HULC triggers autophagy via stabilizing Sirt1 and attenuates the chemosensitivity of HCC cells	Oncogene	Article	2017	273
4	Autophagy promotes hepatocellular carcinoma cell invasion through activation of epithelial-mesenchymal transition	Carcinogenesis	Article	2013	220
5	Inhibition of PI3K/Akt/mTOR pathway by apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells	Biomedicine & pharmacotherapy	Article	2018	215
6	Inhibition of Akt reverses the acquired resistance to sorafenib by switching protective autophagy to autophagic cell death in hepatocellular carcinoma	Molecular cancer therapeutics	Article	2014	213
7	Increased mitochondrial fission promotes autophagy and hepatocellular carcinoma cell survival through the ROS-modulated coordinated regulation of the NFKB and TP53 pathways	Autophagy	Article	2016	213
8	RNA m6A methylation regulates sorafenib resistance in liver cancer through FOXO3-mediated autophagy	EMBO Journal	Article	2020	202
9	Autophagy in liver diseases: Time for translation?	Journal of Hepatology	Article	2019	197
10	Autophagy inhibition suppresses pulmonary metastasis of HCC in mice via impairing anoikis resistance and colonization of HCC cells	Autophagy	Article	2013	190

TCs, total citations.

Table 6

The top 10 co-cited references of autophagy and HCC research.

Rank	Co-Cited references	TCs
1	Takamura A, Komatsu M, Hara T, *et al.* Autophagy-deficient mice develop multiple liver tumors. Genes Dev. 2011;25(8):795-800[15]	91
2	Llovet JM, Ricci S, Mazzaferro V, *et al.* Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90[28]	75
3	Qu X, Yu J, Bhagat G, *et al.* Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest. 2003;112(12):1809-20[76]	62
4	Shi YH, Ding ZB, Zhou J, *et al.* Targeting autophagy enhances sorafenib lethality for hepatocellular carcinoma via ER stress-related apoptosis. Autophagy. 2011;7 (10):1159-72.[99]	62
5	Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;132(1):27-42.[100]	56
6	Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245-55.[101]	50
7	Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell. 2011;147(4):728-41.[102]	50
8	Mizushima N, Yoshimori T, Levine B. Methods in mammalian autophagy research. Cell. 2010;140(3):313-26[37]	49
9	Shimizu S, Takehara T, Hikita H, *et al.* Inhibition of autophagy potentiates the antitumor effect of the multikinase inhibitor sorafenib in hepatocellular carcinoma. Int J Cancer. 2012;131(3):548-57[93]	49
10	Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer. 2017;17(9):528-42.[103]	47

TCs, total citations.

from the United States and France. This distribution underscores the significant contribution of Chinese scholars to the field of autophagy research. The most cited article from this selection was published in 2015 by Wang Y *et al.*[27], affiliated with the Key Laboratory of Infection and Immunity, Chinese Academy of Sciences. Appearing in *Cell Stem Cell*, the study garnered 460 citations and provided insights into how the lncRNA lncTCF7 supports the self-renewal capability of HCC stem cells by engaging the Wnt signaling pathway. This work underscores the crucial role of lncRNAs in tumor growth and proliferation.

In 2013, the journal *Autophagy* published a foundational review by Professor Czaja MJ of the Marion Bessin Liver Research Center at Albert Einstein College of Medicine. This review detailed the role of autophagy in both healthy liver function and liver disease[10], setting a precedent for subsequent research in the field. Moreover, it is noteworthy that 40% of the top 10 co-cited references originated from Japan, reflecting the significant scientific contributions of Japanese researchers within this domain. The document by authors such as Takamura A. and Mizushima N, titled 'Autophagy-deficient mice develop multiple liver tumors'[15], established the importance of autophagy in preventing spontaneous tumor development, particularly in the liver, and highlighted the role of p62 accumulation in tumor progression. Collaborations between Mizushima N and Levine B are central to pivotal works that delve into the methodologies for monitoring and manipulating autophagy in mammalian cells[37]. Additionally, as demonstrated in Figure 8, seven clusters illustrate varying degrees of interdisciplinary collaboration, with '#2 sorafenib inhibit' notably emerging as a research hotspot in recent years.

Research hotspots and frontiers

Identifying research hotspots and frontiers is crucial for comprehending the evolution and direction of a scientific field. Key themes and shifts in research can be elucidated by analyzing recurring keywords. As depicted in Figure 9, keywords serve as indicators of these hotspots and frontiers, directing attention to the most dynamic and influential areas of study.

Hot spot 1: Signaling pathways and mechanisms of HCC and autophagy

In Figure 9, a cluster of keywords includes 'signaling pathway', 'adenosine monophosphate-activated protein kinase (AMPK)', 'AKT', 'EMT', 'metastasis', and 'cancer cell'. These terms underscore the complex and dualistic nature of autophagy within HCC development, as evidenced by a plethora of studies[10,11].

The prosurvival role of autophagy in HCC

Autophagy can support the survival of tumor cells under stress conditions, such as nutrient and oxygen scarcity and the stresses induced by chemotherapy[10,18,19]. Gao *et al.*[38] demonstrated that glycochenodeoxycholate (GCDC) not only enhances the invasion potential of HCC cells but also induces autophagy, suggesting bile acids might promote HCC invasion via autophagy activation. These findings propose bile acid levels as a potential prognostic indicator for HCC patients. Researchers have observed that isoquercitrin (ISO) exposure can diminish cell viability and colony formation, induce apoptosis, and disrupt autophagy through the AMPK/mTOR/p70S6K pathway, offering insights into therapeutic approaches[39]. Additionally, studies have identified genes related to HCC prognosis, such as ATIC, which appears to hamper autophagy while promoting liver cancer cell proliferation, invasion, and metastasis via the AKT/FOXO3 signaling pathway[40].

The tumor-suppressive role of autophagy in HCC

Conversely, autophagy may exert a protective effect during cancer initiation by countering mutated proteins and altered signaling pathways, thus inhibiting malignant transformation[19,20]. Solamargine (SM), a compound derived from traditional Chinese medicine, has been found to hinder HCC cell proliferation and induce both apoptosis and autophagy by targeting LIF/miR-192-5p/CYR61/Akt signaling and modulating the tumor microenvironment[41]. SOCS5, a member of the SOCS protein family, has been associated with poor prognosis in HCC. Its inhibition can reduce HCC cell migration and invasion in vitro via PI3K/Akt/mTOR-mediated autophagy, with dual inhibition of SOCS5 and mTOR amplifying the antimetastatic effect[42]. What is more, autophagy may also promote tumor metastasis by triggering EMT[21,43]. The solid tumor microenvironment, characterized by hypoxia due to rapid tumor growth, can pressure cancer cells to adapt and metastasize[44]. EMT, a central mechanism in solid tumor invasion and metastasis, involves changes in cell behavior and marker expression, such as increased N-cadherin and vimentin and decreased E-cadherin[45,46]. Fluid shear stress has

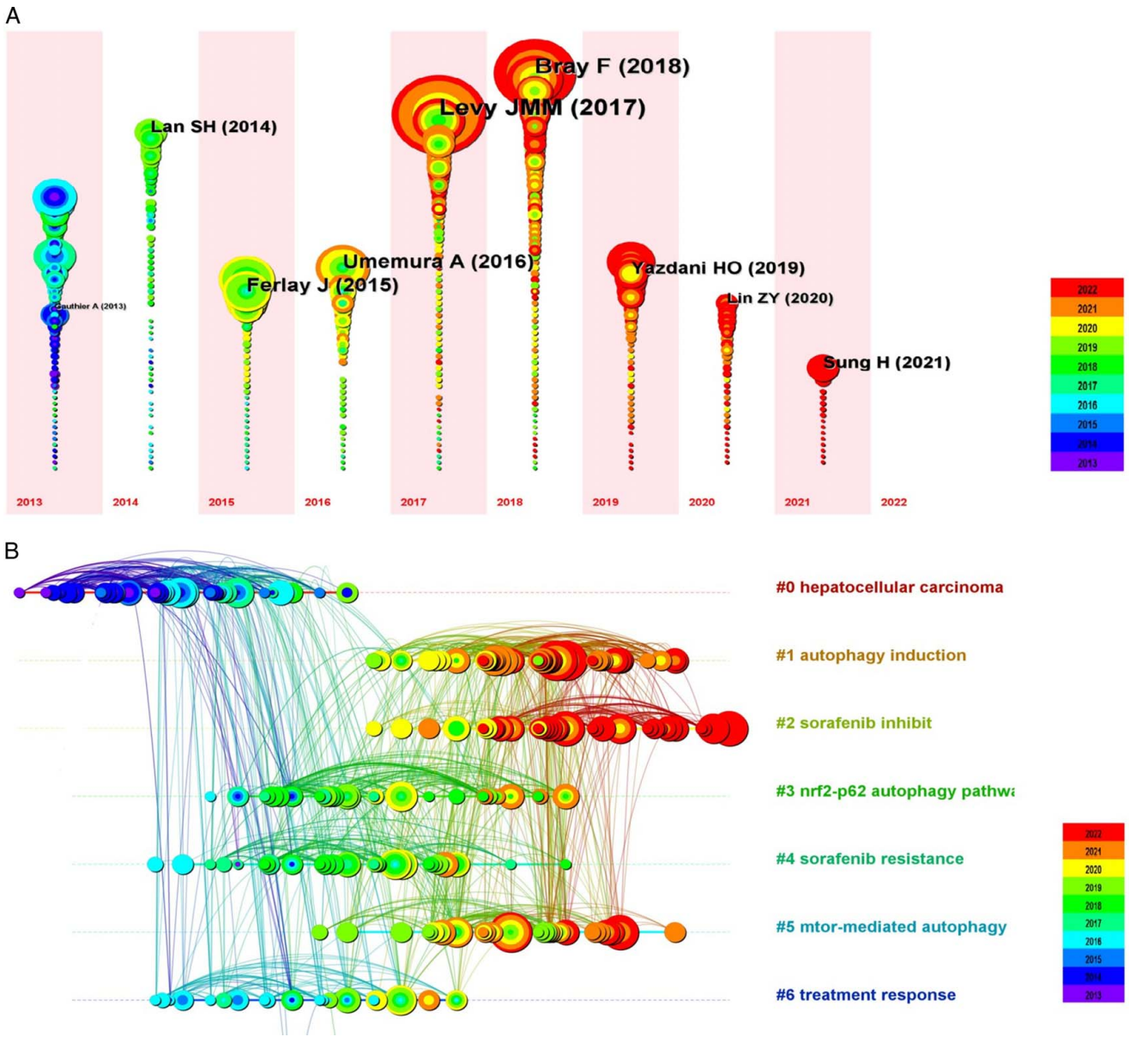

Figure 8. The bibliometric analysis of co-cited references in the HCC and autophagy research. A. The timezone view. B. The timeline view.

been shown to enhance the formation of autophagosomes, upregulate autophagy markers like Beclin-1 and ATG7, and elevate mesenchymal markers, thereby facilitating EMT and the invasion and metastasis of HCC cells[43]. Additionally, sphingosine kinase 1 (SPHK1) can induce EMT by promoting the autophagy-linked lysosomal degradation of CDH1/E-cadherin in HCC cells[47].

Through various signaling pathways, autophagy is implicated in the complex interplay between cell survival, apoptosis, and metastatic processes[48]. These insights underscore the potential of autophagy-related therapeutic targets in HCC and justify the continued exploration into autophagy as a multifaceted process within cancer biology. Over the past decade, researchers have identified several key signaling pathways in HCC that intersect with the process of autophagy. Below is a discussion of some noteworthy pathways.

The AMPK-mTOR pathway

Adenosine monophosphate-activated protein kinase (AMPK) is a key regulator of energy homeostasis, influencing lipid, cholesterol, and glucose metabolism, particularly in the liver, muscle, and adipose tissue[49]. The mammalian target of rapamycin (mTOR) is a central regulator of cell growth, which typically suppresses autophagy when nutrient levels are sufficient[50]. The AMPK-mTOR pathway is critically involved in autophagy regulation[38,49,51]. AMPK can promote autophagy during glucose starvation by directly activating ULK1 (a kinase initiating mammalian autophagy) via phosphorylation at Ser 317 and Ser 777[52]. Conversely, mTOR activity can inhibit ULK1 activation under nutrient-rich conditions by phosphorylating Ser 757, thus preventing its interaction with AMPK[50]. Metformin, a well-known diabetes drug, has been found to activate AMPK, inhibit

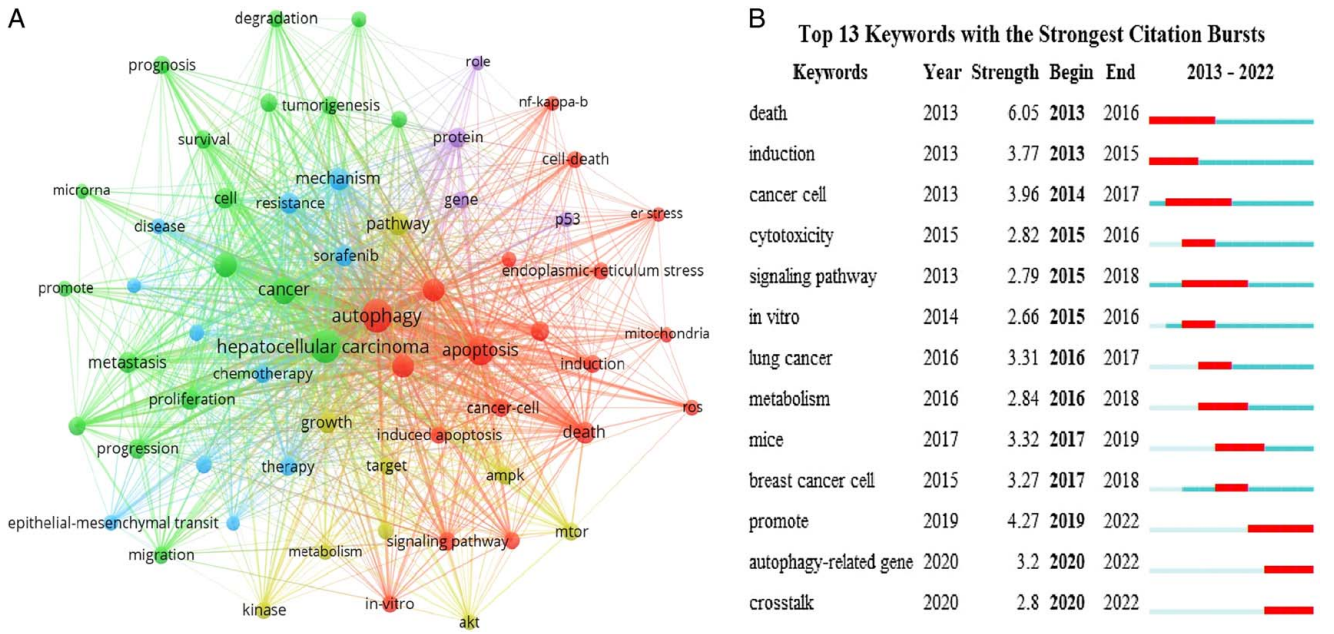

Figure 9. The knowledge map of active keywords (A) and the keywords with the strongest citation bursts (B) in the autophagy and HCC research.

mTOR phosphorylation, induce autophagy, and promote apoptosis in HCC cells through various pathways, including the CEBPD-induced autophagy pathway[53,54].

The PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway is crucial for many cellular functions, including growth and survival, and its inhibition can lead to antitumor effects[50,55–57]. Apigenin, a dietary flavonoid, has demonstrated antioxidant and antitumor properties, and has been shown to inhibit cell proliferation and induce autophagy by suppressing the PI3K/Akt/mTOR pathway[58–60]. Overexpression of SOCS5, a suppressor of cytokine signaling, enhances HCC cell migration and invasion through the inhibition of PI3K/Akt/mTOR-mediated autophagy[42]. Thus, the dual inhibition of SOCS5 and mTOR can amplify autophagy and exert stronger antitumor effects. Other compounds like brusatol and bufotoxin have also been found to induce apoptosis and autophagy by inhibiting the PI3K/Akt/mTOR pathway, highlighting potential therapeutic strategies for HCC[61–63].

The Wnt/β-Catenin pathway

The Wnt/β-catenin pathway is vital for liver homeostasis, regeneration, and carcinogenesis, with 30–40% of HCCs showing aberrations in this pathway[64–66]. This pathway has also been implicated in autophagy regulation[67]. Glypican-3 (GPC3), an HCC marker, is regulated by the Wnt/β-catenin signaling and can be modulated by autophagy. Starvation and rapamycin-induced autophagy decrease GPC3 levels and downstream Wnt target genes in HepG2 cells, while autophagy inhibition can reverse these effects[68,69]. Curcumin has been shown to inhibit the Wnt/β-catenin pathway and reduce GPC3 expression, suggesting a potential treatment avenue[70]. Additionally, autophagy activation has been linked to increased expression of MCT1, which is associated with lactate transport and promotes metastasis and glycolysis in HCC cells[71].

The interplay between autophagy and various signaling pathways in HCC reveals the complexity of cellular regulation and potential targets for therapeutic intervention. The AMPK-mTOR and PI3K-AKT-mTOR pathways are central to autophagy regulation, with substances that modulate these pathways showing promise in preclinical studies. The Wnt/β-catenin pathway also plays a dual role in both tumor promotion and suppression through its relationship with autophagy. Understanding these mechanisms further may pave the way for novel HCC treatments that target autophagy and associated signaling pathways.

Hotspot 2: autophagy-related genes and proteins in HCC

The presence of burst keywords indicates areas of intense research activity and potentially groundbreaking advancements. By tracking these terms, researchers can gage the trajectory of emerging concepts and methodologies that propel the field forward. The cluster of keywords including 'autophagy-related gene', 'Beclin-1', 'Beclin-2', and 'P53' represents a hot spot in HCC research, as depicted in Figure 9B. This indicates a significant trend and growing interest in the roles of specific genes and proteins related to autophagy in HCC.

Beclin-1 and autophagy in HCC

Beclin-1 (BECN1), the mammalian counterpart of yeast Atg6/Vps30, is a pivotal autophagy protein located on human chromosome 17q21, near the BRCA1 gene[72]. BECN1 is essential for the autophagic process, and its role in protecting HCC cells from apoptosis due to starvation has been well-documented[73]. Several studies have also investigated how different proteins and compounds might interfere with BECN1-related pathways or affect its interaction with Beclin-2[74–76]. The JNK/BECN1

signaling pathway is known to be involved in autophagy, and inhibition of JNK has been shown to reduce autophagy and the invasive capacity of HCC cells, as induced by BMP4. This suggests that BMP4-promoted autophagy exacerbates HCC invasion via the JNK/BECN1 pathway[77]. Moreover, tangeretin, a bioactive compound from Chinese herbs, has been found to inhibit HepG2 cell proliferation, migration, and autophagy; these effects are partially reversed by knocking down BECLIN1 expression[78,79]. Tangeretin also affects the JNK1/Bcl-2 pathway, disturbing the interaction between Bcl-2 and BECLIN1, indicating a mechanism through which tangeretin could inhibit HepG2 cell proliferation and migration via JNK/Bcl-2/BECLIN1-mediated autophagy[79].

The role of p53 in autophagy and HCC

The p53 gene is one of the most extensively studied tumor suppressor genes in the context of solid tumors, including HCC. Epidemiological data suggest that p53 mutations are more prevalent in aflatoxin-related HCC than in HCC unrelated to aflatoxin(50 vs.28–42%) and that p53 aberrations are more common in HBV-related HCC compared to HCV-related HCC (45 vs. 13%)[80]. The relationship between p53 and autophagy is complex and bidirectional. On one side, autophagy can suppress p53 by reducing oxidative stress, which is known to activate p53[81]. By eliminating organelles that produce reactive oxygen species (ROS), autophagy limits oxidative stress and consequently p53 activity[81–83]. On the other side, p53 has been shown to activate the transcription of autophagy-related genes such as Ulk1 and Atg7[84,85]. Thus, p53 can both promote and be inhibited by autophagy, depending on the cellular context.

Hotspot 3: targeting autophagy for HCC treatment

The cluster that includes terms such as 'inhibitor', 'sorafenib resistance', 'chemotherapy therapy', and 'crosstalk' highlights the significance of targeting autophagy as a therapeutic strategy for HCC. There is a growing body of research focused on manipulating autophagy either to enhance the efficacy of anticancer treatments or to overcome resistance to existing therapies.

Autophagy promoters in HCC therapy

Autophagy promoters generally work by simulating conditions of starvation or nutrient deprivation[50]. Inhibition of mTOR, which is a key sensor for cell energy status, can induce autophagy in a manner similar to starvation by dephosphorylating Atg13 and overriding the negative feedback mechanism of the PI3K-AKT-mTOR pathway[86]. This approach has been employed with drugs like metformin, which inhibits mTOR phosphorylation and induces autophagy in HCC cells[53], and isoquercitrin, which activates autophagy via the AMPK/mTOR/p70S6K pathway[39].

Apigenin and resveratrol are other examples of compounds that can induce autophagy by inhibiting the PI3K/Akt/mTOR pathway[60,87]. Resveratrol has shown increased BECN1 expression and LC3 II/I ratio, upregulation of p53, and decreased phosphorylated Akt in HCC cells, leading to inhibition of cell proliferation and migration[87]. The dual inhibition of SOCS5 and mTOR further enhances autophagy through the PI3K-AKT-mTOR pathway, exerting additional anticancer effects[42].

Autophagy inhibitors in HCC therapy

On the other hand, autophagy inhibitors work by impeding specific proteins involved in the autophagy pathway or by directly disrupting lysosomal function. For instance, apigenin combined with the autophagy inhibitor 3-MA has been shown to significantly enhance the compound's anticancer effect[60]. Similarly, vitexin inhibits HCC growth by inducing apoptosis and inhibiting autophagy through the JNK-MAPK pathway[88]. However, not all inhibitors of autophagy-related proteins are effective in suppressing autophagy. Pifithrin-α, a p53 inhibitor, has been reported to decrease BECN1 expression but simultaneously increase HCC cell proliferation, invasion, and migration[87].

Sorafenib resistance in HCC

Sorafenib acts by targeting the RAF/MEK/ERK signaling pathway to hinder tumor cell proliferation and blocks VEGFR and PDGFR to inhibit angiogenesis[89]. Resistance to sorafenib has become a pressing issue, compromising the drug's efficacy in treating HCC[90]. Autophagy has been implicated as a factor contributing to sorafenib resistance, with observations that some tumor tissues and sorafenib-resistant HCC cell lines overexpress CD24, which increases PP2A protein production and inactivates the mTOR/AKT pathway, thereby promoting autophagy[91]. Combination therapies that include autophagy inhibitors have shown promise in enhancing the effectiveness of sorafenib[87]. For example, chloroquine, which interrupts autophagic flux by preventing the fusion of autophagosomes with lysosomes, has been found to augment the antitumor effects of sorafenib[92,93]. Additionally, metformin's ability to inhibit mTORC1 and MAPK pathways has been enhanced by sorafenib, leading to greater tumor suppression[53,94]. Inhibitors such as GDC0068, which target Akt, have also been shown to synergistically inhibit growth in sorafenib-resistant HCC cells by converting autophagy from a protective mechanism to one that promotes cell death[95,96]. However, the response to sorafenib varies among HCC cell lines, with some showing increased autophagic flux and others not responding in the same way[97,98]. These differences suggest that the autophagic response is cell-type specific and must be considered when developing therapeutic strategies.

The targeting of autophagy, whether to stimulate or inhibit the process, has emerged as a promising therapeutic approach for HCC. By manipulating autophagy-related signaling pathways or proteins, researchers aim to develop novel strategies to enhance the effectiveness of current treatments, overcome drug resistance, and improve patient outcomes. Understanding the complex role of autophagy in cancer biology is crucial for the creation of targeted therapies. As research progresses, it is likely that additional autophagy modulators, both promoters and inhibitors, will be identified and potentially translated into clinical practice. The goal is not only to deepen our understanding of autophagy and its role in HCC but also to translate this knowledge into more effective therapeutic interventions that can improve patient outcomes, particularly in cases where conventional treatments like sorafenib face resistance.

Conclusions

This manuscript aims to shed light on autophagy in HCC and identify the hotspots through systematic bibliometric analysis

and visualization research. China has emerged as a leader in autophagy research within the HCC field, with significant collaboration between Chinese and American researchers and institutions over the past decades. The study of the mechanisms of autophagy in HCC initiation and progression, as well as the exploration of autophagy-related proteins and genes, remains at the forefront of scientific inquiry. Additionally, the interception of autophagy pathways and the overcoming of sorafenib resistance have crystallized as salient themes within the study of autophagy in HCC in recent years. These discoveries have laid a comprehensive foundation for both clinicians and researchers, offering invaluable perspectives and informing the trajectory of subsequent investigations.

Ethical approval

All data in this study are derived from Web of Science that is an accessible database for all scholars, and the data are reflected in the text of the manuscript, pictures and tables. There is no need for ethical approval.

Consent

All data in this study are derived from Web of Science. Our research does not involve patient or privacy. There is no need for patient or volunteer consent.

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Author contribution

T.H. and J.Z.: drafted the manuscript; K.S. and J.Y.: conducted article retrieval, statistical analysis, and data interpretation; T.H., K.S., J.Y., and J.Z.: critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Research registration unique identifying number (UIN)

All data in this study are derived from Web of Science. Our research does not involve patient or privacy. Therefore, there is no need for research registration unique identifying number (UIN).

Guarantor

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Data availability statement

The data in this study is accessible in the public domain and not of a confidential nature. All the data could be contact with the corresponding author: hetao9208@outlook.com with scientific purpose.

Provenance and peer review

Not applicable.

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