Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2022**; 27(9): 272
https://doi.org/10.31083/j.fbl2709272

Original Research

Global Research Trends and Hotspots of Autophagy in Colorectal Cancer: A 20-year Bibliometric Analysis Based on Web of Science

Peng-Yue Zhao[1,*,†], Xing-Peng Yang[1,†], Ze Fu[1], Tian-Ze Wang[1], Song-Yan Li[1], Xiao-Hui Du[1,*]

[1]Department of General Surgery, First Medical Center of Chinese PLA General Hospital, 100853 Beijing, China
*Correspondence: 15010112665@163.com (Peng-Yue Zhao); duxiaohui301@sina.com (Xiao-Hui Du)
[†]These authors contributed equally.

Academic Editors: Mario Scartozzi, Eleonora Lai, Andrea Pretta and Dario Spanu
Submitted: 12 July 2022 Revised: 27 August 2022 Accepted: 29 August 2022 Published: 29 September 2022

Abstract

Background: Autophagy plays a pivotal role in the progression and management of colorectal cancer (CRC). Recently, numerous articles focusing on the role of autophagy in CRC have emerged. The present study was conducted to provide a comprehensive analysis of the current state and changing trends in the relationship of autophagy and CRC over the past 20 years. **Methods**: The Web of Science Core Collection (WOSCC) was utilized to extracted all publications with respect to autophagy and CRC during 2002–2021. The contributions of various countries/regions, institutions and journals in this field were analyzed, moreover, research hotspots and promising future trends predicted through keywords were identified by the online platform of bibliometrics, CiteSpace and VOSviewer. **Results**: A total of 2418 related publications from 2002 to 2021 were identified and collected. China occupied first place with respect to the number of publications, followed by the USA and South Korea. Shanghai Jiao Tong University published the most papers in this field. Most publications were published in Oncotarget. Additionally, analysis of the keywords identified 4 clusters with various research focuses: "mechanism-related research", "clinical-related research", "tumorigenesis research" and "chemotherapy-related research". The three latest hot keywords in this field were epithelial–mesenchymal transition (EMT), promote and invasion. **Conclusions**: The number of publications and research interest on autophagy and CRC are increasing annually, and the USA had prominent academic positions in the field. Shanghai Jiao Tong University represents a high level of research and the latest progress in this field can be tracked at Oncotarget. Throughout the research history of autophagy and CRC in the past 20 years, previous studies have mainly concentrated on apoptosis and drug resistance in tumor cells, while EMT in regulating tumorigenesis and development of clinical drugs that inhibit tumor invasion through autophagy may be novel hotspots in the future.

Keywords: autophagy; colorectal cancer; bibliometric analysis; EMT; research hotspots

1. Introduction

Colorectal cancer (CRC) ranks third and second in morbidity and mortality, respectively, and is a heavy burden on global health and medical services [1,2]. The latest global cancer statistics indicated that there were 1.9 million new CRC cases and 935,000 reported deaths every year, and pioneering or revolutionary theoretical research to improve the morbidity and mortality of CRC patients is eagerly desired [1]. Autophagy, which was initially proposed by Porter and Ashford [3], is a prevalent process of engulfing, degrading and reusing damaged organelles or misfolded proteins to maintain the homeostasis of the intracellular environment [4,5].

Numerous previous studies have confirmed that autophagy is closely linked to the occurrence, development, metastasis, recurrence and drug resistance of CRC [6–8]. It is widely recognized that autophagy plays a dual role in cancer development with opposing effects, which means that inhibitory and promotive phenomena exist simultaneously [9–11]. For instance, TP53 is a well-known tumor suppressor gene that exerts an indispensable effect in cancer progression, while the protein encoded by it, P53, can suppress mammalian target of rapamycin (mTOR) activity to enhance autophagy and thus inhibit tumor growth [12–14]. In contrast, accumulating evidence suggests that autophagy can also promote tumor growth and lead to chemotherapy drug resistance. Moreover, the oncogenic gene Ras was reported to be induced and trigger autophagy, and the latter could recycle intracellular components to sustain the survival of tumor cells under metabolic stress conditions such as a lack of nutrients or hypoxia [8,15,16].

Although there are numerous studies on the role of autophagy in colorectal tumors, the diversity and complications of these studies may also bring several issues to relevant researchers. For example, what have been recent research hotspots? What is the potential direction of this research in the near future? Fortunately, the advent of bibliometrics may provide crucial support for answering these questions. Bibliometrics is a tool that allows for the qualitative and quantitative analysis of knowledge carriers, including books and literature [17]. Bibliometric analysis provides an opportunity to analyze changing trends in a particu-

lar field on a global scale and to investigate the contribution of countries/regions, institutions, scholars, etc. [18]. Additionally, it is also possible to analyze the research hotspots in the field and forecast future research directions, which makes it a well-accepted method [19].

To perform a comprehensive analysis of the publications on autophagy and CRC, the bibliometric method was applied to analyze changes in the overall trends of publications in this field over the past 20 years and to predict possible future research hotspots. We hope that this study can serve as a reference for researchers and provides some clues for future research.

2. Materials and Methods

2.1 Data Sources and Search Strategies

The science citation index extension (SCIE) is the database that is most commonly used in bibliometric analysis [20,21]. Bibliometric articles need to be analyzed by some software, such as CiteSpace and Vosviewer, and these softwares have strict requirements on the database, which should be Web of Science Core Collection (WOSCC) database, especially the data in SCIE [22,23]. While to our knowledge, other big medical databases like PubMed, SCOPUS and Embase could not generate data types needed for software analysis, so they cannot be used. A comprehensive search of the literature from 2002 to 2021 whose types were limited to only original articles and reviews was carried out through the WOSCC database. We conceived a strategy that combined exploded medical subject heading (MeSH) terms, entry terms and wildcard. Wildcard "*" indicates any group of characters or no character [24]. The search strategy was as follows: TS = (Rectal Neoplasm*) OR TS = (Rectal Tumor*) OR TS = (Rectal Cancer*) OR TS = (Rectum Neoplasm*) OR TS = (Rectum Cancer*) OR TS = (Cancer of the Rectum) OR TS = (Cancer of Rectum) OR TS = (Colorectal Neoplasm*) OR TS = (C Colorectal Tumor*) OR TS = (Colorectal Cancer*) OR TS = (Colorectal Carcinoma*) OR TS = (Colonic Neoplasm*) OR TS = (Colon Neoplasm*) OR TS = (Cancer of Colon) OR TS = (Colon Cancer*) OR TS = (Cancer of the Colon) OR TS = (Colonic Cancer*) AND TS = ((Autophagy) OR TS = (autophag*) OR TS = (Autophagic Cell Death) OR TS = (Chaperone-Mediated Autophagy) OR TS = (Macroautophagy) OR TS = (Microautophagy)) AND LANGUAGE = (English) [25]. To avoid bias arising from the frequent renewal of the database, all data retrieval and collection were accomplished within one day of 26 April 2022. Public databases were the sole source of all information, and no human subjects were-involved in this study, therefore no ethical informed consent was needed. Fig. 1 illustrates the process of publication enrollment and screening in detail.

2.2 Data Collection

Literature screening and data filtering were carried out by two reviewers (PYZ and XPY) independently. Data

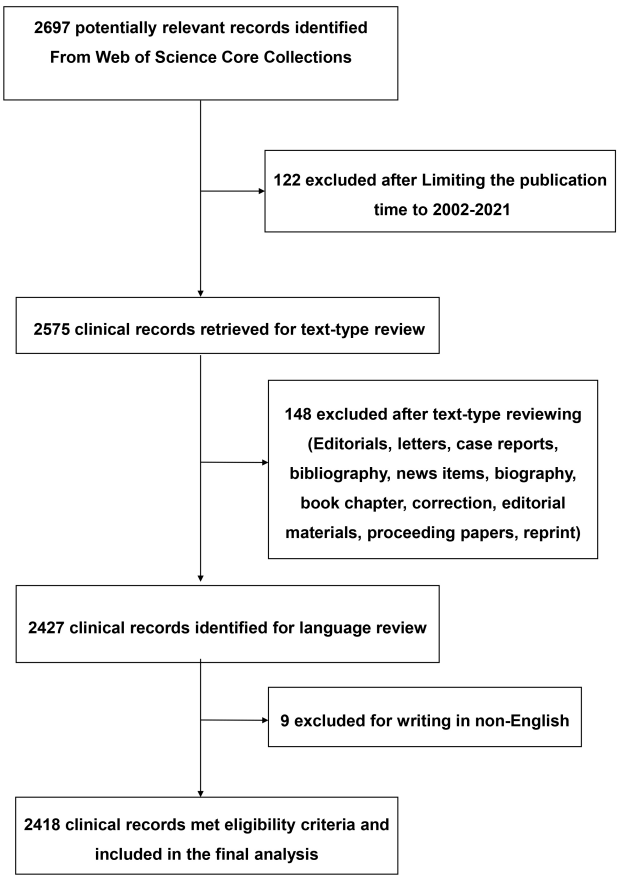

Fig. 1. Flow diagram of research selection and screening.

that were obtained from WOSCC included the title, keywords, date of publication, authors, institutions, country or region, journals, total citations and H-index. Qualitative and quantitative analyses were conducted by VOSviewer (Leiden University, Leiden, Netherlands), Microsoft Excel 2016 (Redmond, Washington, USA), CiteSpace (Drexel University, USA) and the online platform of bibliometrics (http://bibliometric.com/).

2.3 Bibliometric Analysis

Bibliometric analysis provides an opportunity to analyze changing trends in a particular field on a global scale, investigate the contributions from multiple dimensions and analyze the research hotspots in the field and forecast future research directions [26]. All publication characteristics of eligible literature in WOSCC were well documented and described. We gained access to the latest impact factors (IF) of the relevant periodicals by surveying the current edition of JCR (Journal Citation Reports), which is an essential criterion for the evaluation of academic influences [27]. The H-index acquired from WOSCC has been widely accepted for evaluating the scientific contribution of a scholar or a country/region. It is defined as H papers that have been published by a scholar or a country/region and each paper that has been cited at least H times, including self-citations [28]. The number of annual publications and changing

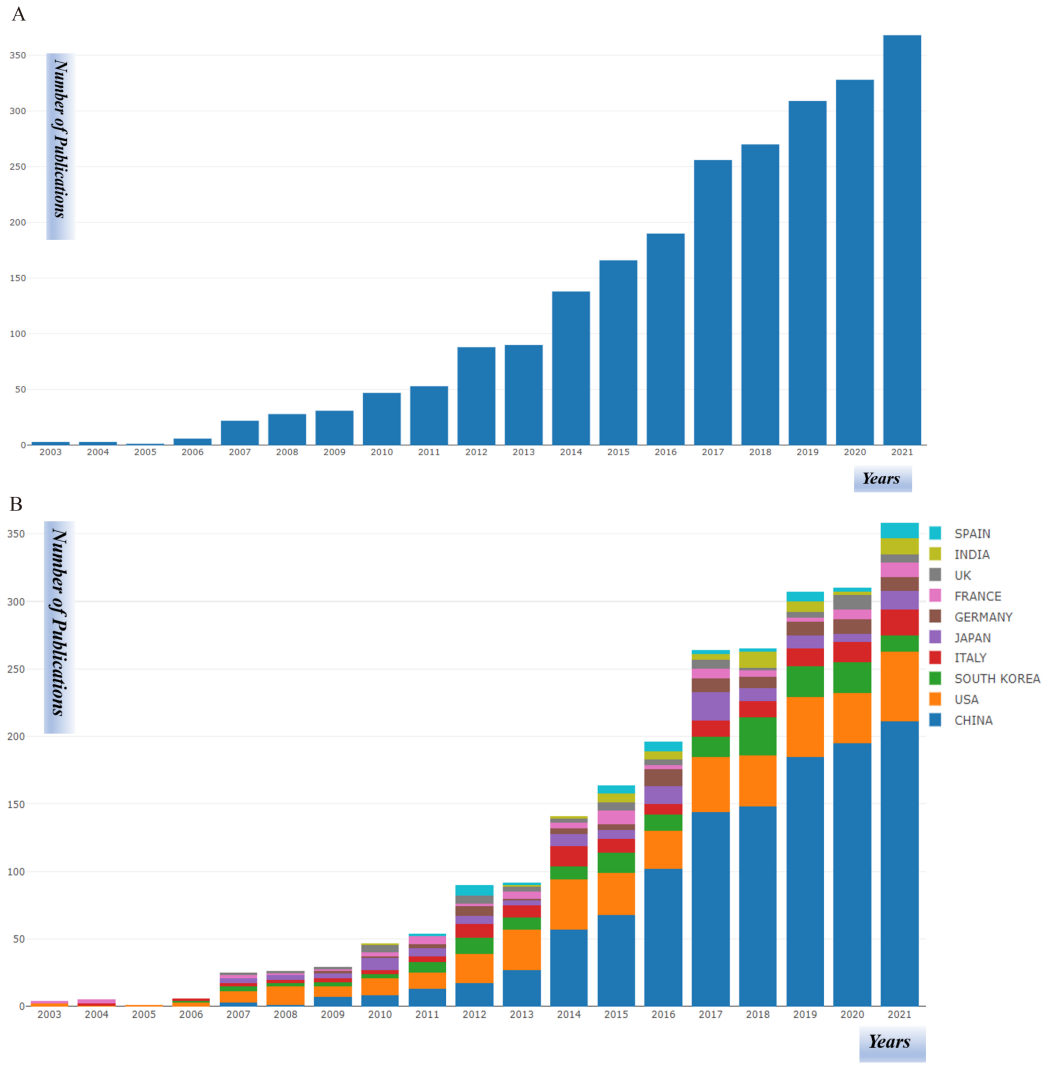

Fig. 2. The number of annual publications on autophagy and colorectal cancer from 2002 to 2021. (A) Global. (B) Top 10 Countries or regions.

trends in different countries/regions were analyzed utilizing the online bibliometrics platform. Keywords extracted from the included literature were divided into different clusters according to the results of cooccurrence analysis by VOSviewer, and marked with various colors according to their appearance time. The relative novelty of keywords was measured by Average Appearance Year (AAY). AAY refers to the average time calculated by integrating the time of the first occurrence and the last occurrence of a certain keyword, which can intuitively reflect the time of the emergence of the keyword in the early or late and the novelty degree. Collaboration analyses on institutions and journals as well as co-occurrence analyses on keywords were performed by CiteSpace. Additionally, the top strongest citation bursts of institutions, journals and keywords were also derived from this software.

The specific parameter settings of Citespace were as follows: Time-slicing was chosen from 2002 to 2021, year per slice, and all options in the term source were selected, node types were selected one at a time, selection criteria (g-index, $g2 \leq k\ Si \leq gci, k \in Z+, k = 25$) [20]. Each node in the figure indicated an observation including country, institution, co-cited literature and keywords.

3 Results

3.1 Global Dynamics of Publications

A total of 2418 studies published from 2002 to 2021 were enrolled based on the inclusion criteria (Fig. 1). The global trend in the number of publications illustrated in Fig. 2A revealed that the annual number of publications related to autophagy and CRC climbed steadily, although there was only a slight increase in 2009, 2011 and 2013 compared to the previous years. The years 2020 (328, 13.6%) and 2021 (368, 15.2%) were the two years with the most relevant publications. It is worth noting that the growth rate accelerated remarkably in 2017. The growth of the top ten countries in terms of the number of articles pub-

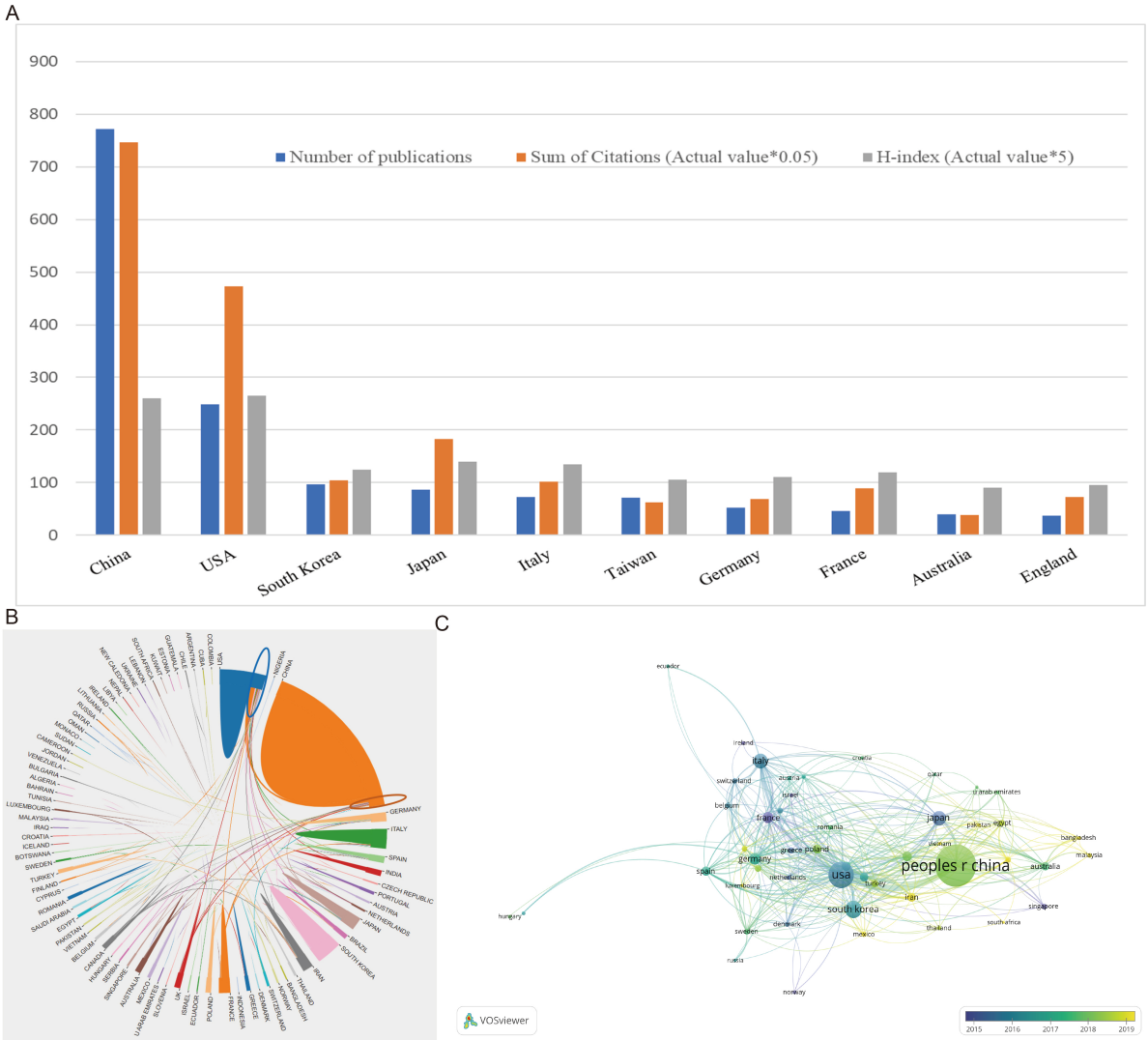

Fig. 3. A visual map of countries/regions associated with autophagy and colorectal cancer. (A) The number of publications, citation frequency (×0.05), and H-index (×5) in the top 10 countries or regions. (B) The cooperation of countries/regions from 2002 to 2021; more lines emanating from a country indicate the closer international cooperation. (C) The distribution of countries/regions is presented according to the appearance of the average time.

lished is shown in Fig. 2B. As the country with the largest number of articles published, China's growth trend is stable and rising, which is basically consistent with the global trend.

3.2 Contribution of Countries/Regions to Global Publications

China ranked first with regard to the number of publications (1093, 45.2%), followed by the United States (425, 17.6%), South Korea (182, 7.5%), Italy (142, 5.9%) and Japan (126, 5.2%). The top 10 countries/regions in terms of the total number of articles published are illustrated in Fig. 3A. From the perspective of literature citation frequency, the top 5 countries in terms of total publication volume during the past 20 years also rank in the top 5 in regard to total citation frequency and H-index, but with a slight change in order. The top 5 countries with the highest total citation frequency were China (25,044 times), the USA (19,495 times), Japan (5326 times), South Korea (5127 times) and Italy (4673 times). Despite China having the highest citation frequency, the H-index of China was 65, which was in second place after the USA. The latter with an H-index of 70, ranked first among all countries.

In addition, we analyzed the collaborative level among countries/regions (Documents ≥5) in this field, and mapped out the cooperation links among countries/regions using VOSviewer. As shown in Fig. 3B, the USA had closer international cooperation than other countries/regions. Additionally, articles published in China were predominantly concentrated in the last three years, which reflected that China has led the advancement of this research field (Fig. 3C).

Table 1. Top 10 institutions published studies related to autophagy and colorectal cancer.

Rank	Institutions	Country	Number of studies	Percentage (N/2418)
1	Shanghai Jiao Tong University	China	63	2.61
2	Sun Yat-sen University	China	62	2.56
3	Zhejing University	China	56	2.32
4	Institut National de la Santéet de la Recherche Médicale	France	48	1.99
5	University of Texas System	USA	46	1.90
6	Central South University	China	44	1.82
7	Fudan University	China	44	1.82
8	Chinese Academy of Sciences	China	41	1.70
9	Nanjing Medical University	China	39	1.61
10	Zhengzhou University	China	38	1.57

Table 2. Top 10 productive journals related to autophagy and colorectal cancer.

Rank	Journal	Studies counts	Percentage (N/2418)	IF
1	Oncotarget	96	3.97	5.17 in 2016
2	Cell Death Disease	71	2.94	9.69
3	Plos One	65	2.69	3.75
4	International Journal of Molecular Sciences	52	2.15	6.21
5	Cancers	47	1.94	6.57
6	Oncology Letters	43	1.78	3.11
7	Autophagy	42	1.74	13.39
8	Oncology Reports	42	1.74	4.14
9	Scientific Reports	40	1.65	5.00
10	Cancer Letters	39	1.61	9.76

3.3 Contribution of Institutions to Research on Autophagy and Colorectal Cancer

Globally, Shanghai Jiao Tong University (63, 2.61%) and Sun Yat-sen University (62, 2.56%) were the two institutions with the most literature published in this field over the last 20 years. Eight of the top 10 institutions with respect to the number of articles published were from China, while the remaining two were the University of Texas System from the USA and the Institut National de la Santé et de la Recherche Médicale (INSERM) from France (Table 1). Then, we conducted the institutional cooperation analysis with CiteSpace to reveal the cooperation between institutions (Fig. 4A).

3.4 Journals Publishing Research on Autophagy and Colorectal Cancer

A total of 537 articles, 22.2% of the entire literature, were published in the top 10 journals by number of publications in the last 20 years. Oncotarget (96, 4.0%), Cell Death Disease (71, 2.9%), Plos One (65, 2.7%), International Journal of Molecular Sciences (52, 2.2%) and Cancers (47, 1.9%) ranked in the top 5, accounting for 13.7% of all publications related to autophagy and CRC (Table 2). Additionally, as shown in Fig. 4B, co-citation analyses on journals revealed that Nature, Nature Reviews Cancer and Autophagy were highly cited journal and located in the center of the co-cited journals.

3.5 Analysis of Cited References

In addition, we listed the top 10 articles in terms of frequency of citations, among which the most cited article entitled "Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment" was conducted by Wang X *et al*. [29] and published in Cell Death Disease in 2013. The total citation and average annual citation frequencies of this study were up to 774 and 77.4, respectively. Another study, titled "*Fusobacterium nucleatum* Promotes Chemoresistance to CRC by Modulating Autophagy", was conducted by Ta Chung Yu *et al*. [30] in 2017 and published in Cell. Despite coming in forth with total citations of 675, it ranked first with an annual average citation frequency of 102.5 among the top 10 most cited articles. Regarding the top 10 papers, Cell Death Disease, Cancer Research and Nature Cell Biology each published two articles, whereas the remaining 4 highly cited articles were published in distinct journals (Table 3).

As shown in Fig. 5A, the co-cited references network was composed of 868 nodes and 2337 links, with a time slice set to 1 year and a period set to 2002–2021. The study entitled "Guidelines for the use and interpretation of assays for monitoring autophagy" published in 2012 was the one which the highest centrality (0.29) [31]. The followed one was the study "Autophagy induction impairs migration and invasion by reversing EMT in glioblastoma cells", which was conducted by Myriam Catalano *et al*. [32] and pub-

Table 3. Top 10 high-cited papers related to autophagy and colorectal cancer.

Title	Corresponding authors	Journal	Publication Year	Total Citations	Average per Year
Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment	X Wang, C He and H Pan	CELL DEATH DISEASE	2013	774	77.4
Autophagic and tumor suppressor activity of a novel Beclin1-binding protein UVRAG	Jae U. Jung	NATURE CELL BIOLOGY	2006	766	45.06
Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth	CraigB. Thompson	CANCER RESEARCH	2007	726	45.38
Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy	Yingxuan Chen, Haoyan Chen, Jie Hong, Weiping Zou and Jing-Yuan Fang	CELL	2017	675	112.5
Quantitative Metabolome Profiling of Colon and Stomach Cancer Microenvironment by Capillary Electrophoresis Time-of-Flight Mass Spectrometry	Tomoyoshi Soga	CANCER RESEARCH	2009	668	47.71
p38 and JNK MAPK pathways control the balance of apoptosis and autophagy in response to chemotherapeutic agents	Qin Zhang, Chao He and Hongming Pan	CANCER LETTERS	2014	558	62
New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate	Jeong-a Kim	REDOX BIOLOGY	2014	436	48.44
Cytosolic FoxO1 is essential for the induction of autophagy and tumour suppressor activity	Wei-Guo Zhu	NATURE CELL BIOLOGY	2010	412	31.69
Differential effects of endoplasmic reticulum stress-induced autophagy on cell survival	Xiao-Ming Yin	JOURNAL OF BIOLOGICAL CHEMISTRY	2007	383	23.94
CircHIPK3 promotes colorectal cancer growth and metastasis by sponging miR-7	Shukui Wang	CELL DEATH DISEASE	2018	379	75.8

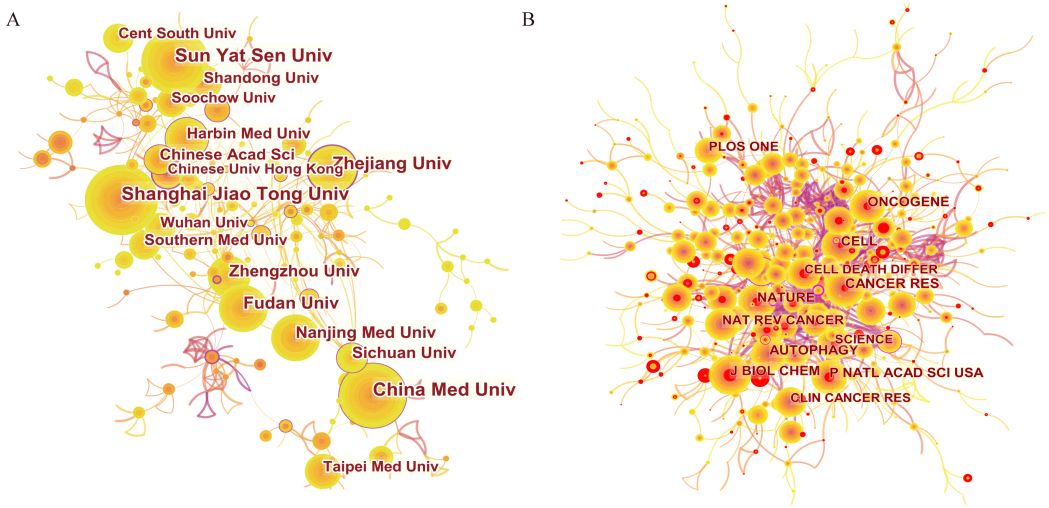

Fig. 4. The contributions of institutions and journals in autophagy and colorectal cancer. (A) Global institutions collaboration analysis. The nodes represent institutions, and the lines mean connection between them. The publication number is proportional to the size of nodes, and the thickness of the connecting line is proportional to the degree of cooperation. The nodes with outermost purple circle indicate a higher centrality. From 2002 to 2021, the color changed from deep to light yellow. (B) Journals co-citation analysis. The nodes represent journals, and the lines mean citations between them. The publication number is proportional to the size of nodes, and the thickness of the connecting line is proportional to the degree of citations. The nodes with outermost purple circle indicate a higher centrality while the red core of the nodes represents stronger citation bursts. From 2002 to 2021, the color changed from deep to light yellow.

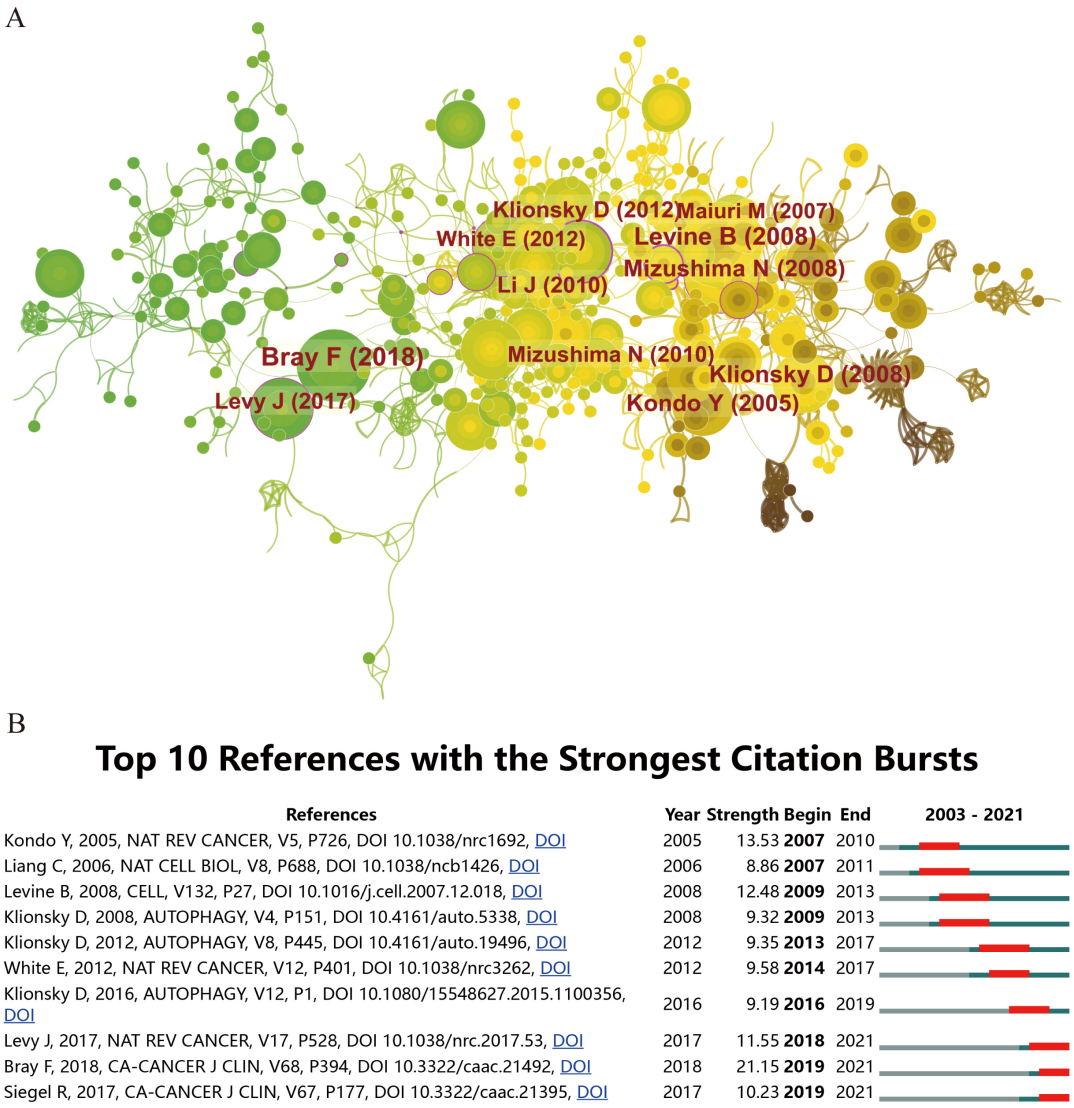

Fig. 5. A CiteSpace network visualization of co-cited references regarding autophagy and colorectal cancer. (A) Network visualization diagram of cited references. The nodes represent references, and the lines mean citations between them. The citation number is proportional to the size of nodes. The nodes with outermost purple circle indicate a higher centrality. From 2002 to 2021, the color changed from brown to green. (B) Top 10 references with the strongest citation bursts related to autophagy and CRC. The blue line represents the time axis, and the red portion on the blue time axis represents the interval at which the burst was found, including the start year, end year, and burst duration.

lished in Molecular Oncology. Additionally, we listed the top 10 references with strongest citation bursts. The study "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries" by Freddie Bray *et al*. [33] topped the list with the citation burst of 21.15 (Fig. 5B).

3.6 Analysis of Keywords and Research Hotspots on Autophagy and Colorectal Cancer

Ninety-seven keywords were extracted from the title and abstract of 2418 articles that met the criteria, and co-occurrence analysis was performed via VOSviewer. By means of mapping analysis, we divided the keywords with more than 40 co-occurrences into four clusters with different research focuses: Cluster 1 (mechanism-related research, red), Cluster 2 (clinical-related research, green), Cluster 3 (tumorigenesis research, blue) and Cluster 4 (chemotherapy-related research, yellow). For each keyword, the size of the circle indicates its co-occurrence frequency (Fig. 6A).

Keywords within Cluster 1 included autophagy (1586 times), apoptosis (937 times), inhibition (315 times), death (273 times), growth (264 times) and so on. In Cluster 2, colorectal-cancer (489 times), cancer (246 times), proliferation (227 times), metastasis (158 times) and breast-cancer (148 times) were the keywords with the highest frequen-

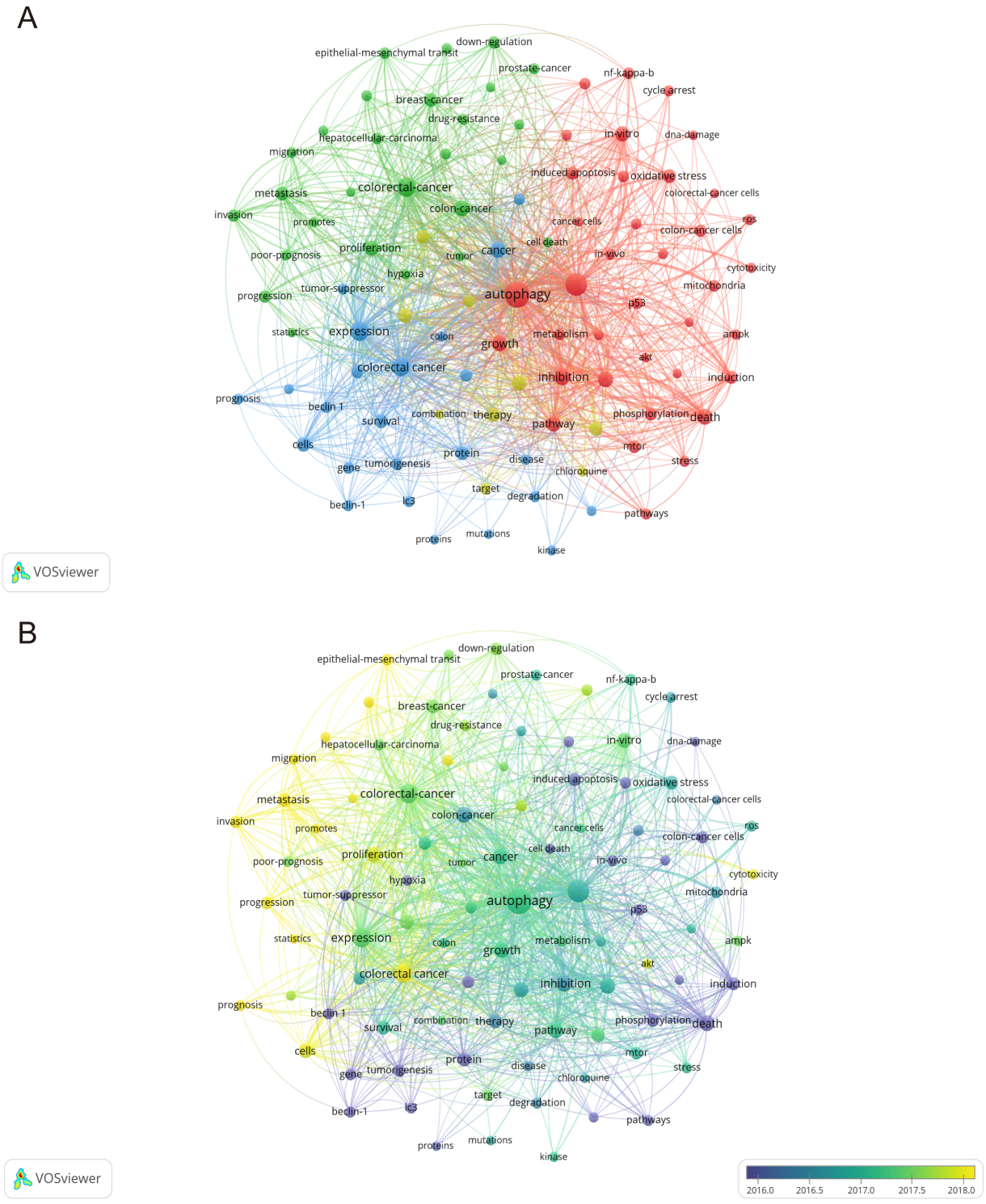

Fig. 6. Analysis of keywords in publications of autophagy and colorectal cancer. (A) Mapping of the keywords in the area. The words were divided into 4 clusters in accordance with different colors generated by default: mechanism-related research (red), clinical-related research (green), tumorigenesis research (blue) and chemotherapy-related research (yellow). The circle with a large size represents the keywords that appeared at a high frequency. (B) Distribution of keywords was presented according to the appearance for the average time. The blue color represents an early appearance and the yellow color represents a recent appearance. Two keywords co-occurred if they both occurred on the same line in the corpus file. The smaller the distance between two keywords, the larger the number of co-occurrences of the keywords.

cies. In Cluster 3, the dominant keywords were expression (488 times), colorectal cancer (450 times), cells (176 times), protein (163 times) and survival (142 times). In Cluster 4, the following keywords were frequently mentioned: colon-cancer (218 times), resistance (177 times), therapy (161 times), mechanisms (155 times) and chemotherapy (139 times). Detailed information on all included keywords is listed in **Supplementary Table 1**. We colored each keyword by VOSviewer according to its time of appearance, with blue representing a relatively early emergence and yellow representing a more recent emergence (Fig. 6B). During the early stage of the exploration of CRC and autophagy, "macroautophagy" (Cluster 3, keyword AAY 2013.6), "beclin-1" (Cluster 3, keyword AAY 2014.4), "activated protein-kinase" (Cluster 1, keyword AAY 2014.5) and "*in-vivo*" (Cluster 1, keyword AAY 2015.2) were the primary research focus.

Moreover, analysis of novel keywords within Cluster 1 (mechanism-related research) revealed that "cytotoxicity" (AAY 2017.9), "akt" (AAY 2017.9) and "signaling pathway" (AAY 2017.7) might be research highlights. In the "clinical-related research" cluster, the latest key words were "epithelial-mesenchymal transition" (AAY 2019.3) and "invasion" (AAY 2019.2), occurring 84 times and 96 times respectively. In Cluster 3 (tumorigenesis research), "prognosis" (AAY 2018.0) and "colorectal cancer" (AAY 2018.2) were listed as relatively novel keywords, which were mentioned 65 and 450 times respectively. For Cluster 4 (chemotherapy-related research), "resistance" (AAY 2017.5) and "target" (AAY 2017.4) were considered popular keywords. Of note, sometimes, using 5 co-occurrences might reveal new words that were not mentioned before, and it could be trending. Therefore, we all provided a list of keywords with more than 5 co-occurrences (**Supplementary Table 2**), which revealed that "tcga" (AAY 2020.6), "prognostic signature" (AAY 2020.5), "lncrna" (AAY 2020.3), "metal-complexes" (AAY 2020.3) and "ferroptosis" (AAY 2020.3) were the top five novel keywords.

Finally, we utilized CiteSpace to explore top 25 keywords with the strongest citation bursts in the past 20 years. In the first decade, "cell death" (burst intensity of 6.11), "death" (burst intensity of 11.18) and "beclin 1" (burst intensity of 11.13) were the focus of research in this filed. While in the next 10 years, "invasion" (burst intensity of 15.39), "long noncoding rna" (burst intensity of 8.42) and "migration" (burst intensity of 4.65) gradually became the research frontiers of autophagy in CRC (Fig. 7). The Citespace Metadata and VOSviewer Metadata of bibliometric analysis in this present research can be found in **Supplementary File 3**.

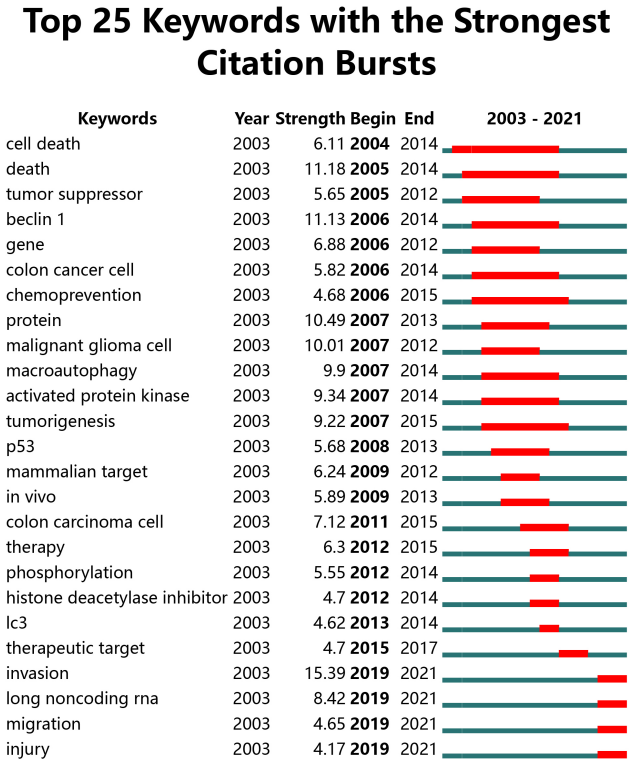

Fig. 7. Top 25 keywords with the strongest citation bursts related to autophagy and CRC. The blue line represents the time axis, and the red portion on the blue time axis represents the interval at which the burst was found, including the start year, end year, and burst duration.

4. Discussion

4.1 Research Trends on Autophagy and Colorectal Cancer

Fig. 2 illustrates that the number of annual publications in this area increased steadily each year, although there was only a slight increase in 2009, 2011 and 2013 compared to the previous years. In the decade between 2011 and 2020, the number of annual publications in this field rose continuously. The steady increase in the number of publications in this field indicated that it has been a research hotspot worldwide. Given the strong growth in annual publications in 2021 compared to the year before, we speculate that this area will remain a focus of research in the coming years. When we had a closer view of the top 5 countries in terms of total publications, most of them showed a slight increase even decrease in 2011 compared to the previous year, which explained to some extent the slight increase of global publications in the corresponding year. Moreover, it is worth noting that the growth rate accelerated significantly in 2017. The 2016 Nobel Prize in Physiology or Medicine was awarded to Japanese scientist Yoshinori Ohsumi for his research on autophagy, which undoubtedly triggered a climax of autophagy research. Therefore, it was comprehensible that there was a surge in autophagy- and CRC-related articles in 2017 for the periodicity of the publications.

China, the USA and South Korea were the top 3 countries in terms of total publications, which have also conducted the most research in field of CRC and autophagy. China was a late starter in this field, only beginning to publish studies in 2010, but it has far surpassed other countries in terms of numbers by publishing 1093 studies in the following years [34]. China was not as far ahead in the academic impact of research in this field as it was in the volume of publications. With an H-index of 65, China was in second place behind the United States. Among the top 10 countries with the most publications over the past 20 years, the United States was the first to publish research in the field, which in part explains its extraordinary academic influence [35]. Basic medical research in the US seems to have a superior environment and conditions, characterized by cutting-edge equipment, professional researchers, sufficient funds and extensive academic interaction. These strengths have helped the USA become a leading force in this domain.

China occupied first and second place with regard to total citations and the H-index, respectively. Its huge volume of publications, three times that of the second place, may be partly accountable for its number one ranking in terms of citation frequency. Despite its late start in this field, China's H-index is basically on par with that of the United States. Whether the quantitative advantage can be translated into a qualitative advantage will be the key factor for China's H-index to surpass the United States. Not only in China, a slight discrepancy between the quality and quantity of research also existed in South Korea. South Korea ranked third in terms of the total number of relevant studies, while its citation frequency and H-index ranked only fourth and fifth, respectively. But it has to be said that South Korea's performance in this field has been quite outstanding in being able to stand out among numerous developed countries. Although the high incidence of gastrointestinal tumors in South Korea provides an inherent advantage for domestic researchers to conduct research, the unremitting exploration of Korean researchers is also one of the indispensable factors for South Korea to be at the forefront of the world in this field. China's academic influence in this field has increased significantly since 2014, as evidenced by the fact that 6 of the top 10 cited articles were produced by Chinese researchers independently and one by a collaboration between Chinese and American researchers. As Fig. 3 shows, China and the USA had the most intense academic exchanges and cooperation with other countries. Within the context of global collaborative commons, an increasing number of important studies accomplished by multinational researchers working together will emerge in the future. Therefore, it is highly likely that future pioneering breakthroughs in this field will come in the form of cooperation between China or the USA and other countries.

Among the top 10 institutions in terms of the number of articles published, the top three were all from China, and the fifth was from the USA, which was in line with the leading position of both countries in this field. Half of the top 10 most frequently cited articles were published by the top 10 institutions, with two articles contributed by Zhejiang University in China. If the United States intends to continue its excellent academic standing in this area, more elite institutions will be required to participate in relevant research in the future. China, with a multitude of high-quality institutions, needs to improve international cooperation to jointly promote research associated with autophagy and CRC worldwide.

Regarding the journals, Oncotarget (Not Found, IF = 5.17 in 2016) published 96 relevant studies, far more than any other journals. Unfortunately, it was excluded from SCI and it remains uncertain whether it should be reintroduced in the future. Undoubtedly, due to the exclusion from SCI, numerous novel research or new methods in this field may not be published in the journal, and the impact will remain until Oncotarget is re-included by SCI. Cell Death Disease (IF = 9.69), Plos One (IF = 3.75), International Journal of Molecular Sciences (IF = 6.21) and Cancers (IF = 6.57) were the other major journals publishing relevant articles that we recommend researchers in the field to focus on to keep track of hot topics and advances. Of note, although Nature (IF = 69.50), Nature Reviews Cancer (IF = 69.80) and Autophagy (IF = 13.39) were not top 10 productive journals, they were all highly cited journal, which to some extent reflected their strict requirements for the quality of articles included. In addition, Frontiers in Pharmacology, Journal of Cancer and Frontiers in Oncology were journals with high citation influence in recent three years, reflecting their strong interests in the research of autophagy and CRC.

4.2 Research Focuses on Autophagy and Colorectal Cancer

Articles with the leading citation frequency have a huge academic influence on research in certain fields. Details of the top 10 cited publications are shown in Table 3. The research entitled "Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment" has been cited 774 times since its publication, and is the most frequently quoted study on CRC and autophagy. This research was published in Cell Death Disease (IF = 9.69) in 2013, and its corresponding authors were X Wang, C He and H Pan from China [29]. In this review, Sui X *et al*. [29] summarized the molecular mechanism and drug development status of cancer chemotherapy resistance detailedly from the perspective of autophagy. This research deeply analyzed the potential drug value and existing problems of autophagy in the treatment of chemotherapy resistance, and innovatively proposed that autophagy inhibitors may play unexpected effects of anticancer therapies for cancer patients, which might be the first demonstration of a close relationship between autophagy and chemotherapy re-

sistance in various cancers including CRC. The second and third most highly quoted studies were published in Nature cell Biology (IF = 28.21) and Cancer Research (IF = 13.31), respectively. A previous study identified a novel coiled–coil UV irradiation resistance associated gene (UVRAG), which was a positive regulator of the Beclin-PI 3 kinase class III (PI3KC3) complex. Normally, the interaction of UVRAG and Bcl-2 fine-tuned Beclin1-PI3KC3 activity and modulate autophagy within a homeostatic range. However, genetic mutations of Beclin1 and UVRAG in colon cancer cells could reduce their proteins expressions and then attenuated the degree of autophagy, which eventually led to the invasion and progression of colon cancer. Overall, this study illuminated that autophagy is a vital cellular regulatory mechanism guiding tumor-cell growth, which enriched the molecular regulatory mechanism network of Beclin-1 mediated autophagy [36]. The latter used paired isogenic colon cancer cell lines ($p53^{+/+}$ and $p53^{-/-}$) to investigate the effects of metformin, a diabetes drug, on tumor growth from the perspective of metabolic adaptations [37]. Monica Buzzai *et al*. [37] proposed that metformin treatment could significantly block the metabolic transformation process of $p53^{-/-}$ colon tumor cells, in other words, metformin had selective toxicity to p53-deficient cells. Noteworthily, this study provided new evidence that metformin could be used to treat cancer, as well as new options for patients harboring p53-deficient tumors that were resistant to chemotherapy or radiotherapy. Of note, the study titled "*Fusobacterium nucleatum* Promotes Chemoresistance to CRC by Modulating Autophagy" ranked first with an annual average citation frequency of 102.5 among the top 10 most cited articles [30]. This study found that *Fusobacterium nucleatum* could activate the autophagy pathway and lead to cancer chemoresistance by targeting toll-like receptor 4 (TLR4) and myeloid differentiation factor 88 (MYD88) innate immune signals and specific microRNAs, suggesting that measuring and targeting *Fusobacterium nucleatum* might be useful for patient prognosis and management. Taken together, the majority of the top 10 most cited articles focused on exploring the mechanisms underlying the link between autophagy and CRC and the role it played in the treatment course.

The latest hot topic keyword was "epithelial-mesenchymal transition" (Cluster 2, AAY is 2019.3). EMT is the process by which cells lose their epithelial properties and acquire mesenchymal properties, which was first described in embryogenesis [38]. It's well known that EMT is a multifaceted and reversible biological process involving cellular, genetic, physiological, metabolic and any other changes [39]. Moreover, as a highly regulated and orchestrated process, EMT possesses a body of factors or effectors to ensure the normal and correct execution of its own function, such as GSK3β, TGF-β, vimentin and so on [40–42]. Similarly, EMT plays a critical role in tumor progression, metastasis, and drug resistance in CRC. Growing evidence from preclinical and early clinical studies suggests that EMT markers may serve as prognostic predictors and potential therapeutic targets for CRC [43]. Therefore, translating basic research on EMT in colorectal tumors into effective clinical applications will be a research hotspot in the field of autophagy and CRC.

In fact, the vast majority of novel keywords appearing after 2018 were from the "clinical-related research" cluster, such as "statistics" and "drug-resistance". As Fig. 6A illustrates, the "mechanism-related research" cluster and "clinical-related research" cluster were the two main segments of research in this field, both of which had a relatively closer connection to the "chemotherapy-related research" cluster and a relatively weak relationship to the "tumorigenesis research" cluster. Moreover, a number of emerging keywords were identified from the "clinical-related research" cluster, which indicated that the research focus was moving in the direction of this cluster. Moreover, "autophagy", "apoptosis" and "colorectal cancer" were the three most prominent keywords and were located in the central area of the network, implying a strong connection with the rest of the keywords. Recently, a study revealed that knockdown of *Rb1cc1*, an autophagy-related gene, enhanced TNF-mediated apoptosis and consequently boosted the tumor-killing effect of T cells [44]. A positive effect of autophagy inhibitors in antitumor therapy has been demonstrated in recent research [45]. With the trend of research shifting towards the "clinical-related research" cluster, the clinical application of autophagy inhibitors which block or delay tumor invasion will be another possible hotspot for future research.

4.3 Strengths and Limitations

We extensively and systematically searched the WoSCC database and conducted a comprehensive and objective analysis of research developments in the field of CRC and autophagy over the past 20 years. To the best of our knowledge, this is the first study to perform a scientometric analysis of literature related to CRC and autophagy. The contributions of top journals, authors, countries/regions, institutions, and research topics and clusters were identified. Moreover, the analysis and prediction of possible future research hotspots were carried out from the perspective of bibliometrics, which might provide reference proposals for potential academic cooperation, funding-orientation guidance, and even scientific prizes in this field. Nonetheless, some limitations are still inevitable. First, only English articles were enrolled, which means that some potentially valuable non-English literature was ignored and excluded from our research. Second, the types of research that met the inclusion criteria were limited to articles and reviews. Thus, letters, conference papers and books, which may have academic impact were excluded. Third, the literature published before 2002 could not be found in the current research. Forth, due to the inherent characteristics and strict requirements on the database of

bibliometric tools, we only searched SCIE database, and relevant literatures from other databases were not included in this research. Fifth, we used keywords that appear at least 40 times to cluster and calculate AAY to predict future research hotspots in this field, while keywords less than 40 times are ignored, which affects the accuracy of our prediction to a certain extent. Finally, bibliometrics is a quantitative analysis method that does not provide a comprehensive assessment of the quality of published studies.

5. Conclusions

The number of publications and research interest on autophagy and CRC are increasing annually, and China published the most articles while the USA had the most prominent academic positions in the field. Shanghai Jiao Tong University represents a high level of research and the latest progress in this field can be tracked at Oncotarget. Moreover, the high quality or top high-cited articles can be found in Nature, Nature Reviews cancer and Autophagy. Throughout the research history of autophagy and CRC in the past 20 years, previous studies have mainly concentrated on apoptosis and drug resistance in tumor cells, while EMT in regulating tumorigenesis and development of clinical drugs that inhibit tumor invasion through autophagy may be novel hotspots in the future.

Abbreviations

CRC, colorectal cancer; WOSCC, Web of Science Core Collection; EMT, epithelial-mesenchymal transition; mTOR, mammalian target of rapamycin; SCI-E, Science Citation Index-Expanded; TS, topic science; IF, impact factor; JCR, Journal Citation Reports; AAY, average appearing year; INSERM, Institut National de la Santé et de la Recherche Médicale; UVRAG, UV irradiation resistance associated gene; PI3KC3, PI 3 kinase class III; TLR4, toll-like receptor 4; MYD88, myeloid differentiation factor 88.

Author Contributions

XHD and PYZ conceptualized, supervised, and edited the manuscript. PYZ and XPY extracted all data and performed the bibliometric analyses. ZF, TZW and SYL undertook and refined the searches. PYZ and XPY codrafted the paper. All authors contributed to and revised the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81871317) and the Key Project of Military Medical Innovation Program (No. 18CXZ025).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2709272.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394–424.

[3] Ashford TP, Porter KR. Cytoplasmic Components in Hepatic Cell Lysosomes. Journal of Cell Biology. 1962; 12: 198–202.

[4] Wirawan E, Berghe TV, Lippens S, Agostinis P, Vandenabeele P. Autophagy: for better or for worse. Cell Research. 2012; 22: 43–61.

[5] Eskelinen E. New insights into the mechanisms of macroautophagy in mammalian cells. International Review of Cell and Molecular Biology. 2008; 266: 207–247.

[6] White E. Deconvoluting the context-dependent role for autophagy in cancer. Nature reviews Cancer. 2012; 12: 401–410.

[7] White E. The role for autophagy in cancer. Journal of Clinical Investigation. 2015; 125: 42–46.

[8] Guo JY, Chen H, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, *et al*. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes & Development. 2011; 25: 460–470.

[9] Oh DS, Lee HK. Autophagy protein ATG5 regulates CD36 expression and anti-tumor MHC class II antigen presentation in dendritic cells. Autophagy. 2019; 15: 2091–2106.

[10] Pietrocola F, Bravo-San Pedro JM, Galluzzi L, Kroemer G. Autophagy in natural and therapy-driven anticancer immunosurveillance. Autophagy. 2017; 13: 2163–2170.

[11] Li Y, Feun L, Thongkum A, Tu C, Chen S, Wangpaichitr M, *et al*. Autophagic Mechanism in Anti-Cancer Immunity: Its Pros and Cons for Cancer Therapy. International Journal of Molecular Sciences. 2017; 18: 1297.

[12] Sakanashi F, Shintani M, Tsuneyoshi M, Ohsaki H, Kamoshida S. Apoptosis, necroptosis and autophagy in colorectal cancer: Associations with tumor aggressiveness and p53 status. Pathology - Research and Practice. 2019; 215: 152425.

[13] Inoue T, Hayashi Y, Tsujii Y, Yoshii S, Sakatani A, Kimura K, *et al*. Suppression of autophagy promotes fibroblast activation in p53-deficient colorectal cancer cells. Scientific Reports. 2021; 11: 19524.

[14] Güllülü Ö, Hehlgans S, Rödel C, Fokas E, Rödel F. Tumor Suppressor Protein p53 and Inhibitor of Apoptosis Proteins in Colorectal Cancer-A Promising Signaling Network for Therapeutic Interventions. Cancers. 2021; 13: 624.

[15] Strohecker A, Guo J, Karsli-Uzunbas G, Price S, Chen G, Mathew R, *et al*. Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors. Cancer Discovery. 2013; 3: 1272–1285.

[16] Bhatt V, Khayati K, Hu Z, Lee A, Kamran W, Su X, *et al*. Autophagy modulates lipid metabolism to maintain metabolic flexibility for Lkb1-deficient KRAS-driven lung tumorigenesis. Genes & Development. 2019; 33: 150–165.
[17] Dabi Y, Darrigues L, Katsahian S, Azoulay D, De Antonio M, Lazzati A. Publication Trends in Bariatric Surgery: a Bibliometric Study. Obesity Surgery. 2016; 26: 2691–2699.
[18] Zhao PY, Xia Y, Tao ZB, Li SY, Mao Z, Yang XP, *et al*. Global Research Status of Multiple Organ Dysfunction Syndrome During 2001-2021: A 20-Year Bibliometric Analysis. Frontiers in Medicine. 2022; 9: 814381.
[19] Sugimoto CR, Ahn Y, Smith E, Macaluso B, Larivière V. Factors affecting sex-related reporting in medical research: a cross-disciplinary bibliometric analysis. The Lancet. 2019; 393: 550–559.
[20] Ma L, Ma J, Teng M, Li Y. Visual Analysis of Colorectal Cancer Immunotherapy: A Bibliometric Analysis From 2012 to 2021. Frontiers in immunology. 2022; 13: 843106.
[21] Ke L, Lu C, Shen R, Lu T, Ma B, Hua Y. Knowledge Mapping of Drug-Induced Liver Injury: A Scientometric Investigation (2010–2019). Frontiers in Pharmacology. 2020; 11: 842.
[22] Peng C, Kuang L, Zhao J, Ross AE, Wang Z, Ciolino JB. Bibliometric and visualized analysis of ocular drug delivery from 2001 to 2020. Journal of Controlled Release. 2022; 345: 625–645.
[23] Mao Z, Liu C, Chen S, Zhu Z, Kang H, Zhou F. A bibliometric analysis of exertional heat stroke research in Web of Science. Military Medical Research. 2016; 3: 31.
[24] Wu H, Zhou Y, Wang Y, Tong L, Wang F, Song S, *et al*. Current State and Future Directions of Intranasal Delivery Route for Central Nervous System Disorders: A Scientometric and Visualization Analysis. Frontiers in Pharmacology. 2021; 12: 717192.
[25] Yao R, Ren C, Wang J, Wu G, Zhu X, Xia Z, *et al*. Publication Trends of Research on Sepsis and Host Immune Response during 1999-2019: a 20-year Bibliometric Analysis. International Journal of Biological Sciences. 2020; 16: 27–37.
[26] Zhang J, Yang X, Fang J, Cheng Q, Ding H, Sun Y, *et al*. Evolution of associating liver partition and portal vein ligation for staged hepatectomy from 2012 to 2021: a bibliometric analysis. Review. International Journal of Surgery. 2022; 103: 106648.
[27] Eyre-Walker A, Stoletzki N. The assessment of science: the relative merits of post-publication review, the impact factor, and the number of citations. PLoS Biology. 2013; 11: e1001675.
[28] Hirsch JE. An index to quantify an individual's scientific research output. Proceedings of the National Academy of Sciences. 2005; 102: 16569–16572.
[29] Sui X, Chen R, Wang Z, Huang Z, Kong N, Zhang M, *et al*. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. Cell Death & Disease. 2013; 4: e838.
[30] Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, *et al*. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. Cell. 2017; 170: 548–563.e16.
[31] Klionsky DJ, Abdalla FC, Abeliovich H, Abraham RT, Acevedo-Arozena A, Adeli K, *et al*. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy. 2012; 8: 445–544.
[32] Catalano M, D'Alessandro G, Lepore F, Corazzari M, Caldarola S, Valacca C, *et al*. Autophagy induction impairs migration and invasion by reversing EMT in glioblastoma cells. Molecular Oncology. 2015; 9: 1612–1625.
[33] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394–424.
[34] Xiong H, Guo X, Bu X, Zhang S, Ma N, Song J, *et al*. Autophagic cell death induced by 5-FU in Bax or PUMA deficient human colon cancer cell. Cancer Letters. 2010; 288: 68–74.
[35] Ellington AA, Berhow MA, Singletary KW. Inhibition of Akt signaling and enhanced ERK1/2 activity are involved in induction of macroautophagy by triterpenoid B-group soyasaponins in colon cancer cells. Carcinogenesis. 2006; 27: 298–306.
[36] Liang C, Feng P, Ku B, Dotan I, Canaani D, Oh B, *et al*. Autophagic and tumour suppressor activity of a novel Beclin1-binding protein UVRAG. Nature Cell Biology. 2006; 8: 688–698.
[37] Buzzai M, Jones RG, Amaravadi RK, Lum JJ, DeBerardinis RJ, Zhao F, *et al*. Systemic Treatment with the Antidiabetic Drug Metformin Selectively Impairs p53-Deficient Tumor Cell Growth. Cancer Research. 2007; 67: 6745–6752.
[38] Zhang N, Ng AS, Cai S, Li Q, Yang L, Kerr D. Novel therapeutic strategies: targeting epithelial–mesenchymal transition in colorectal cancer. The Lancet Oncology. 2021; 22: e358–e368.
[39] Nieto MA, Huang R, Jackson R, Thiery J. EMT: 2016. Cell. 2016; 166: 21–45.
[40] Côme C, Magnino F, Bibeau F, De Santa Barbara P, Becker KF, Theillet C, e*t al*. Snail and Slug Play Distinct Roles during Breast Carcinoma Progression. Clinical Cancer Research. 2006; 12: 5395–5402.
[41] Derynck R, Akhurst RJ, Balmain A. TGF-beta signaling in tumor suppression and cancer progression. Nature Genetics. 2001; 29: 117–129.
[42] Toiyama Y, Yasuda H, Saigusa S, Tanaka K, Inoue Y, Goel A, *et al*. Increased expression of Slug and Vimentin as novel predictive biomarkers for lymph node metastasis and poor prognosis in colorectal cancer. Carcinogenesis. 2013; 34: 2548–2557.
[43] Thiery JP, Acloque H, Huang RYJ, Nieto MA. Epithelial-Mesenchymal Transitions in Development and Disease. Cell. 2009; 139: 871–890.
[44] Young TM, Reyes C, Pasnikowski E, Castanaro C, Wong C, Decker CE, *et al*. Autophagy protects tumors from T cell–mediated cytotoxicity via inhibition of TNFα-induced apoptosis. Science Immunology. 2020; 5: eabb9561.
[45] Kinsey C, Camolotto S, Boespflug A, Guillen K, Foth M, Truong A, *et al*. Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nature Medicine. 2019; 25: 620–627.