Review Article

Hotspots and development frontiers of circRNA based on bibliometric analysis

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ABSTRACT

Background and purpose: Circular RNAs (circRNAs) are a big group of members of the non-coding RNA family following long non-coding RNA and microRNA. They play a regulatory role in many biological processes. Analyzing their current research status and future development trends is conducive to a more comprehensive understanding of circRNAs and contributes to the dedication to the biological field.

Methods: The literature on circRNA from 2000 to 2021 in the Web of Science Core Collection of the Web of Science database with “circular RNA” as the subject was searched. R Studio’s Bibliometrix package and biblioshiny software were used for publication trend analysis, citation analysis, keyword analysis, author analysis, research institution analysis, source analysis, country analysis, and collaboration analysis for all documents and highly cited documents.

Results: From 2000 to 2021, 3,186 circRNA-related articles were published worldwide, of which 193 were highly cited. The number of published articles had shown an explosive increase after 2013. These articles were mainly from Chinese research institutions and authors, but the country with the highest average number of citations per year in highly cited documents was Germany. Scientific research institutions came from countries represented by Germany, USA, China, Australia and Canada all had different degrees of cooperation. The theme and key points of the research had evolved over time from expression to the role and mechanism of circRNA in diseases, especially in cancer. CDR1as, circFOXO3, circHIPK3, circITCH, circMTO1, circSMARCA5 and circZNF609 are circRNAs that are mainly studied currently, their studies mainly involve cell biology, biological functions and cancer. The future research direction and trend would still be the application of circRNA in diseases.

Conclusion: The basic situation and development trend of circRNA related research we described provide a direction for future research.

1. Introduction

Circular RNAs (circRNAs) are RNAs with special circular structure formed by covalently joining the 5′ end and 3′ end of a linear RNA precursor through a reverse splicing mechanism. As early as the 1970s, circRNAs were first discovered in RNA viruses [1,2]. However, it is considered to be a garbage sequence caused by mistranslation due to its low expression abundance. At the beginning of this century, the research of circRNA has gradually attracted attention while only sporadic reports were shown limited by the level of sequencing technology. With the continuous improvement and development of second-generation sequencing, the important functions of circRNA have gradually been recognized by the public since Menczak et al. [3] revealed that circRNA was widely present in animal cells. Recent years, especially in the past five years, the number of research on circRNA increases explosively. Researchers have not only made outstanding contributions in revealing the formation, characteristics, regulation, mechanism of function, and elimination of circRNA [4–7], but also clarified the important role of...
circRNA in cell biology, including proliferation, apoptosis, aging, etc. [8–12]. On the other hand, researchers have also discovered that circRNA plays an important role in diseases of many systems, including the nervous system, digestive system, circulatory system, respiratory system, urinary system, and motor system [13–18], especially its outstanding position in cancer [19,20], which made us deeply realize the value of circRNA. Therefore, what are the research contents and directions of circRNA in the past 20 years? What is the current research status of circRNA? Where will circRNA’s research go in the future? The answers to these questions are of great help to the research of circRNA.

Bibliometric analysis is a discipline that uses document system and measurement characteristics as the research object, and uses mathematics, statistics and other measurement methods to explore certain structures, characteristics and laws of science and technology [21]. Through literature statistics, we can analyze the research content and research status of a certain research field well, and predict the future development direction, which has high reference value for scientific researchers. Therefore, we used this method to conduct a statistical analysis of all articles and highly cited (H-cited) articles published in the past 20 years with circRNA as the main research content, including main information, the number of articles published each year, the annual citations, the main keywords, the sources, the authors, the institutions and countries, the evolution and trend of the themes, the cooperation relationship of the studies, circRNAs that are mainly studied currently, etc. The article is going to describe the basic situation and development trend of circRNA-related research and provide direction for research in this field by revealing these contents.

2. Data and methods

2.1. Data

The relevant literature of circRNA in the Web of Science Core Collection of the Web of Science (WoS) database was searched and collected. The search strategy was: (((((((((((TI=(circRNA)) OR TI=(circular RNA)) OR TI=(circRNA*)) OR TI=(circular noncoding RNA)) OR TI=(circular nonprotein-coding RNA)) OR TI=(circular nonprotein-coding RNA)) OR TI=(circular untranslated RNA)) OR TI=(circular untranslated RNA)) OR TI=(circular untranslated RNA)) AND PY=(2000–2021)) AND DT=(Article)) AND LA=(English). The document type was limited to article, the language was English, and the time was set from 2000 to 2021. A total of 3,186 documents were finally retrieved, among which 193 were highly cited (H-cited) documents. H-cited papers were defined as papers that have been cited in the top 1% in the last 10 years. The complete record of each article, including title, abstract, keywords, publication year, author, nationality, journal name, research direction, publishing organization, and references, were downloaded from the Web of Science database in BibTex file format.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

The publication year of the literature was from January 1, 2000 to September 30, 2021; the language of the literature was English; the type of the literature was articles; the research topic of the literature was circRNA.

![Fig. 1. Annual publication and citation of articles related to circRNA. A) annual scientific production of total published articles; B) annual scientific production of H-cited published articles; C) average article citations per year of total published articles; D) average article citations per year of H-cited published articles.](image-url)
2.2.2. Exclusion criteria

The types of documents were conferences and reports; the documents did not use circRNA as the research topic; non-English circRNA related documents.

2.2.3. Statistics and visual analysis

R Studio’s Bibliometrix package and biblioshiny software [22,23] were used to analyze the main information of all published articles and H-cited articles, including the amount of articles published each year, the annual citation situation, the main keywords, the sources, the authors, the institutions and countries, and the subject terms evolution and trends, the cooperative relationships. All index frequency was measured by number of documents. Cooperation index means the average number of authors in co-authored articles. Keywords plus means the keywords related to the original article added by WoS while the authors did not add, in order to increase the hit rate of the article under related topics. Trend topics parameters: field was keywords plus, world minimum frequency was 5, number of words per year was more or equal to 5. Thematic evolution and thematic map parameters: field was key words plus, number of words was more or equal to 250, minimum cluster frequency (per thousand docs) was more or equal to 5, weight index was inclusion index weighted by word occurrences and minimum weight index was more or equal to 0.1.

3. Results

3.1. Main information of the published articles

From 2000 to 2021, a total of 3,186 circRNA-related articles were published, of which 193 were H-cited. Among all published articles, there were a total of 650 sources (Journals, Books, etc.), average years from publication was 1.79, average citations per documents was 31.43, average citations per year per doc was 7.583, and the number of keywords plus, author’s keywords, authors, co-authors per document was...
Of all H-cited articles published, there were 83 sources (Journals, Books, etc.), average years from publication was 3.66, average citations per documents was 271.5, average citations per year per doc was 49.2, and the number of keywords plus, author’s keywords, authors, co-authors per document was 487, 392, 1,154, 9.19, respectively, the collaboration index was 1.97.

Fig. 3. Citation of H-cited published articles related to circRNA. A) top 20 most local cited documents; B) top 20 most local cited authors; C) top 20 most local cited sources; D) 14 most cited countries (average citations per year).

Fig. 4. Co-occurrence network for the keywords in the H-cited literature. Cluster 1 was biological characteristics of circRNA (green part), cluster 2 was biological function of circRNA (blue part), cluster 3 was application of circRNA as a biomarker (red part). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
3.2. Annual articles and citations

The number of circRNA-related articles published every year from 2000 to 2013 was less than 10, and no related article was even published in 2005 and 2008. The amount of articles published in 2014 and afterwards had almost increased in an explosive manner and continues to grow. The number of circRNA-related articles published increased from 14 in 2014 to 960 in 2020. Since the total number of articles in 2021 has not yet appeared, it is expected to continue to increase or remain basically the same (Fig. 1A). The average number of articles cited per year was up and down, with the highest number being 118.89 in 2013 (Fig. 1C). In H-cited articles, the earliest article appeared in 2011, with only one article published in this year. The year with most published articles was 2017, reaching 42 (Fig. 1B). The average number of articles cited per year was 210.48 in 2013 (Fig. 1D).

3.3. Sources, authors, institutions and main keywords of the articles

Among all the indexes with the most published articles in all articles, the top 5 journals were BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, AGING-US, EUROPEAN REVIEW FOR MEDICAL AND PHARMACOLOGICAL SCIENCES, SCIENTIFIC REPORTS, CANCER MANAGEMENT AND RESEARCH, with number of 97, 77, 76, 66 and 65, respectively (Fig. 2A). The top 5 authors were Zhang Y, Wang Y, Li Y, Li X, and Wang J, with number 204, 186, 183, 174, and 172, respectively (Fig. 2C). The top 5 institutions were Nanjing Med Univ, Fudan Univ, Sun Yat Sen Univ, China Med Univ and Harbin Med Univ, with number of 615, 384, 347, 264 and 252, respectively (Fig. 2E). And the top 5 related keywords were expression, proliferation, cancer, invasion, growth, with the number of occurrences were 851, 472, 441, 359 and 331, respectively (Fig. 2G). In the H-cited articles, the top 5 journals were CANCER LETTERS, MOLECULAR CANCER, NUCLEIC ACIDS RESEARCH, SCIENTIFIC REPORTS, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, with number of 9, 9, 8, 8 and 7, respectively (Fig. 2B). The top 5 authors were Li J, Li X, Zhang Y, Wang X and Chen Y, with number of 14, 13, 12, 11 and 10, respectively (Fig. 2D). The top 5 institutions were Fudan Univ, Nanjing Med Univ, Ningbo Univ, Harbin Med Univ and Sun Yat Sen Univ, with number of 62, 58, 29, 28 and 27, respectively (Fig. 2F). And the top 5 related keywords were expression, reveals, biogenesis, abundant, gene, with the number of occurrences were 71, 38, 37, 30 and 27, respectively (Fig. 2H).

3.4. Authors, sources, institutions and keywords of highly cited articles

Among all the H-cited articles with most cited times, the top 5 articles were “Memczak S, 2013, NATURE” [3], “Jeck WR, 2013, RNA” [24], “Ashwal-Fluss R, 2014, MOL CELL” [25], “Salzman J, 2012, PLOS ONE” [26], “Salzman J, 2013, PLOS GENET” [27], the number of local citations were 129, 93, 65, 61 and 58, respectively (Fig. 3A). The top 5 institutions were Rajewsky N, Salzman J, Wang P, Brown P and Memczak S, the number of citations were 255, 166, 157, 150 and 137, respectively (Fig. 3B). The top 5 authors were Rajewsky N, Salzman J, Wang P, Brown P and Memczak S, with number of 255, 166, 157, 150 and 137, respectively (Fig. 3C). The top 5 journals were SCIENTIFIC REPORTS, CANCER LETTERS, NUCLEIC ACIDS RESEARCH, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, and PLOS ONE, with number of 9, 9, 8, 8 and 7, respectively (Fig. 3D). And the top 5 related keywords were expression, reveals, biogenesis, abundant, gene, with the number of occurrences were 71, 38, 37, 30 and 27, respectively (Fig. 3E).
Fig. 6. Cooperative relationship of published articles. A) authors cooperative relationship in total published articles; B) authors cooperative relationship in H-cited published articles; C) affiliations cooperative relationship in total published articles; D) affiliations cooperative relationship in H-cited published articles; E) countries cooperative relationship in total published articles; F) countries cooperative relationship in H-cited published articles.
in 2000–2015 to abundant, microRNAs, and expression in 2016–2021 (Fig. 5A). In the H-cited literature, themes have evolved from cells, genome, expression, messenger-RNA, reveals, gene, identification in 2000–2015 to biogenesis, transcription, expression, cancer and circular RNA in 2016–2021 (Fig. 5B). In the thematic map of all articles, themes between the first and second quadrants were absolute, biogenesis, circular RNAs, identification, reveals, between the second and third quadrants were microRNAs, activation, differentiation, mechanisms, and noncoding RNA, located in the fourth quadrant were expression, proliferation, cancer, invasion and growth (Fig. 5C). In the thematic map of H-cited articles, themes in the first quadrant were reveals, absolute and gene, in the second quadrant were apoptosis, squamous-cell carcinoma and autophagy, in the third quadrant were expression, carcinoma and biomarker, and in the fourth quadrant were cancer, growth and proliferation (Fig. 5D). In all the literature, the trend topics in the past two years were ranked in order of prevention, oncogene, expression, proliferation, cancer, invasion and growth (Fig. 5E). In the highly cited literature, the trend topics in the past two years were ranked in the order of circular RNA, invasion, migration, hepatocellular-carcinoma, cell proliferation (Fig. 5F).

### 3.6. Cooperation

The cooperation network of authors, institutions, and countries in all published articles and H-cited articles was analyzed. The size of the dots in the figure represents the amount of articles published by the authors in this field, and the thickness of the lines represents the closeness of cooperation between authors. The results showed that among all published articles, the top 5 authors with the most partnerships were Li Y, Li X, Wang Y, Zhang Y and Li J (Fig. 6A, Table 2); the top 5 institutions with the most partnerships were Fudan Univ, Nanjing Med Univ, Shanghai Jiao Tong Univ, Peking Univ, and Southern Med Univ (Fig. 6C, Table 3); the top 5 countries for the number of published articles were China, USA, Germany, Canada and Spain, with number of published articles 2,735, 129, 54, 24, and 24 (Table 4), the proportions of multiple country publications were 0.0706, 0.3023, 0.3519, 0.75, 0.3333, respectively (Fig. 7A, Table 4); the top 5 countries with the most partnerships were China, USA, Germany, Denmark and Australia (Fig. 6E, Table 5); the top 5 cooperation relationship of countries were from China to USA, from China to Canada, from China to Australia, from USA to Germany, and from China to Germany, the number of articles published were 152, 33, 83, 83, 83, respectively (Fig. 3B). The top 5 sources were Nature, Cell, Nucleic Acids Res, Mol. Cell and PLOS ONE, and the number of citations were 431, 403, 309, 243 and 217, respectively (Fig. 3C). The 5 top countries with the most average article citations per year were Germany, USA, Austria, Italy and Canada, with a total number of citations per year of 844, 531, 309, 243 and 217, respectively (Fig. 3C). The top 5 countries with the most average article citations per year were Germany, USA, Austria, Italy and Canada, with a total number of citations per year of 844, 531, 309, 243 and 217, respectively (Fig. 3C).

### 3.5. Theme evolution and trend

In all the published literature, thematic evolution has gradually developed from mechanism, reveals, gene, DNA, expression, and model...
Table 4
Top 20 countries with the most published articles.

| Countries with the most published articles | Total articles | SCP | MCP | MCP_Ratio | Country | Articles | SCP | MCP | MCP_Ratio |
|------------------------------------------|----------------|-----|-----|-----------|---------|---------|-----|-----|-----------|
| China                                    | 2735           | 2542| 193 | 0.07      | China   | 144     | 124 | 20  | 0.14      |
| USA                                      | 129            | 90  | 39  | 0.30      | USA     | 19     | 14  | 5   | 0.26      |
| Germany                                  | 54             | 35  | 19  | 0.35      | Germany | 12     | 6   | 6   | 0.50      |
| Canada                                   | 24             | 6   | 18  | 0.75      | Canada  | 4      | 1   | 3   | 0.75      |
| Spain                                    | 24             | 16  | 8   | 0.33      | Italy   | 3      | 1   | 2   | 0.67      |
| Italy                                    | 22             | 10  | 12  | 0.55      | Denmark | 2      | 1   | 1   | 0.50      |
| Japan                                    | 21             | 20  | 1   | 0.05      | Israel  | 2      | 2   | 0   | 0         |
| Denmark                                  | 19             | 13  | 6   | 0.32      | Austria | 1      | 1   | 0   | 0         |
| India                                    | 18             | 15  | 3   | 0.17      | France  | 1      | 0   | 1   | 1         |
| Australia                                | 15             | 8   | 7   | 0.47      | India   | 1      | 1   | 0   | 0         |
| France                                   | 15             | 6   | 9   | 0.60      | Japan   | 1      | 1   | 0   | 0         |
| Iran                                     | 14             | 11  | 3   | 0.21      | Netherlands | 1     | 0   | 1   | 1         |
| Netherlands                              | 11             | 6   | 5   | 0.45      | Singapore | 1     | 1   | 0   | 0         |
| Malaysia                                 | 9              | 4   | 5   | 0.56      | Spain   | 1      | 0   | 1   | 1         |
| Russia                                   | 8              | 8   | 0   | 0.00      | Korea   | 7      | 7   | 0   | 0.00      |
| Korea                                    | 7              | 7   | 0   | 0.00      | Switzerland | 7    | 2   | 5   | 0.71      |
| Australia                                | 7              | 3   | 4   | 0.57      | United kingdom | 3 | 1   | 0   | 0         |
| India                                    | 5              | 2   | 3   | 0.60      | Brazil  | 5      | 5   | 0   | 0.00      |

Tips: SCP: single country publications, MCP: multiple country publications.

Fig. 7. Countries with the highest number of published articles related to ci-circRNA. A) total published articles; B) H-cited articles.

Table 5
Top 20 countries with collaboration.

| countries with collaboration | Total articles | H-cited articles |
|-----------------------------|----------------|------------------|
| Node                        | Cluster | Betweenness | Node                | Cluster | Betweenness |
| China                       | 1       | 116.0        | Germany             | 2       | 30.5        |
| USA                         | 1       | 97.6         | USA                 | 1       | 18.6        |
| Germany                     | 3       | 74.1         | China               | 1       | 9.5         |
| Denmark                     | 3       | 32.3         | Australia           | 2       | 0.4         |
| Australia                   | 2       | 27.9         | Canada              | 1       | 0           |
| Netherlands                 | 3       | 3.5          | Japan               | 1       | 0           |
| France                      | 3       | 3.1          | Italy               | 2       | 0           |
| United kingdom              | 3       | 0.8          | Israel              | 2       | 0           |
| Italy                       | 3       | 0.4          | Argentina           | 2       | 0           |
| Canada                      | 1       | 0.2          | Sweden              | 2       | 0           |
| Spain                       | 3       | 0.1          | United kingdom      | 2       | 0           |
| India                       | 1       | 0            |                      |         |             |
| Malaysia                    | 1       | 0            |                      |         |             |
| Poland                      | 1       | 0            |                      |         |             |
| Pakistan                    | 1       | 0            |                      |         |             |
| New zealand                 | 1       | 0            |                      |         |             |
| Sudan                       | 1       | 0            |                      |         |             |
| Japan                       | 2       | 0            |                      |         |             |
| Iran                        | 2       | 0            |                      |         |             |
| Singapore                   | 2       | 0            |                      |         |             |
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4. Discussion

Since 2000, thousands of articles that are obviously related to circRNA have been published. According to the main information of the published articles, each article is cited 7,583 times per year on average, each of H-cited articles is cited even 49.2 times per year, indicating that circRNA has been one of the focus of attention in the research field in the past 20 years. This phenomenon has become more obvious after 2013, especially Memczak et al. [3] revealed that circRNA is widely present in animal cells and may function through miRNA sponge adsorption. The important role of circRNA in biology is gradually recognized, and researchers began to pay attention to the mechanism study of circRNA. After Jeck et al. [24] revealed that circRNA has special ALU repeats, and Zhang et al. [28] revealed that circRNA loops through complementary sequences, research on the structural characteristics of circRNA and the mechanism of circular structure formation began to gain attention. The number of circRNA articles published reaches nearly 1000 per year, these articles give us a deep understanding of the characteristics and the biological function of circRNA in disease research.

The main journals that publish circRNA are comprehensive journals related to RNA biology and cancer, and the publishing organization are mainly Chinese university research institutions, indicating that Chinese researchers have made major contributions in the field of circRNA research. However, when sorted by the number of citations, this situation has changed. The published articles mainly come from top comprehensive journals such as Nature and Cell. The main authors of the published articles are mainly non-Chinese scholars, and the source countries are mainly Germany, the United States, Australia, Italy and Canada. It shows that although authors and institutions from China have published a large number of circRNA-related articles, lack of leading articles is a big shortcoming. This phenomenon is especially manifested in the fact that Chinese authors pay more attention to the biological role of circRNA in cancer and other diseases, rather than studying the mechanism and function of circRNA itself. Of course, there are also a few articles from Chinese researchers that are also very meaningful. For example, articles represented by the Chen LL team on the mechanism of circRNA are also researches with relatively high scientific value [29–31].

From the evolution and trend of the themes, we can see that the research topic of circRNA has gradually developed from the expression and abundance analysis to the biogenesis, transcription and function mechanism of circRNA, such as microRNA sponge in the past five years. Research of circRNA’s identification and abundance, biogenesis, and its function such as influencing cell apoptosis and autophagy has been well developed. The functions of circRNA in cancer cells such as proliferation, invasion, growth and migration are still the most important and promising study themes. This is especially manifested in hepatocellular carcinoma research. Of course, we need to be soberly aware that Chinese research occupies a dominant position in all research, and the published research is mostly circRNA and cancer-related research, which has led to this research trend-oriented. More in-depth and valuable research such as the new function and the mechanism of circRNA formation and function are still worth exploring.

The five main countries with multi-country cooperative scientific research are China, USA, Germany, Denmark, and Australia. Among them, China and the United States have the highest number of cooperative publications. The number of articles published jointly by China and the United States are the most. Although China ranks first in the number of articles published, the proportion of articles on multi-country cooperation is only 0.07, which is significantly less than that of the other four countries. In the H-cited literature, the proportion of China’s cooperation with other countries has increased significantly, indicating that multi-country cooperation may increase the value of research.

Currently, studies of circRNAs involve cell biology, biological functions, and disease (especially cancer) are still cited mostly. CDR1as, circFOXO3, circHIPK3, circITCH, circMTO1, circSMARCA5, and...
5. Conclusion

This article analyzes the research of circRNA from expression analysis to biological function and mechanism in the past 20 years, and proposes that the function and mechanism of circRNA in many diseases remain an area worth exploring in the future.
including cancer are still important research directions in the future. Multi-country and multi-team cooperation will help to make breakthroughs in the field of circRNA research.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Chunlei Zhang, Yindong Kang and Feiyan Kong contributed equally to this work. Chunlei Zhang, Yindong Kang and Feiyan Kong carried out the literature and statistical analysis, and wrote the article. Qi Yang helped edit and correct the manuscript. Dehui Chang conceived the ideas for the article and helped draft the manuscript. Qi Yang, Chunlei Zhang, and Dehui Chang provided funding support. All of the authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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