Bibliometric Analysis of Studies on Tumor Organoids

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Research

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Abstract

**Background:** Organoid is an artificially grown mass of cells or tissues, which is similar to an organ. It can replicate the complexity of an organ and can be used for gaining a better understanding of diseases. In this study, the hot spots of "organoids" were classified into 6 categories and 10 aspects, and organoids used for studying genetic mechanisms, drug effect, and metabolism of tumors showed the greatest potential for future development.

**Methods:** A total of 1550 articles relevant to organoid in tumor research field were recruited as research samples. High-frequency words and text/co-word matrix were constructed by BICOMB software. gCLUTO software was applied to analyze the matrix by double-clustering and visual analysis subsequently to identify the hotspot in this area.

**Results:** We constructed a text and co-word matrix composed of 21 high-frequency words and 1550 articles and generated a hotspot “peak map” based on double-clustering analysis. The strategic coordinates approach was used to assess the research prospects of each hotspot and the connections between these hotspots.

**Conclusions:** In this study, we classified the hot-spots of “organoid” into 6 categories and 10 aspects. Calculation and analysis revealed that the field of tumor organoid shows a slight trend of polarization, and organoid for studying the genetic mechanisms, drug effects and metabolism of tumor shows the greatest potential for future development.

Introduction

The organoid is an artificially grown mass of cells or tissues in vitro, which contains multiple types of cells to mimic its corresponding in vivo organ[1]. On the one hand, an organoid is used to study the development of normal organs, including brain, kidney, adenohypophysis, cerebellum, hippocampus, stomach, lung, thyroid, small intestine, liver, prostate, and mammary gland. On the other hand, the organoid is also used to mimic the development of multiple diseases, such as infectious diseases, hereditary diseases, and tumors[2].

An organoid provides a new insight for understanding the disease, particularly in the field of tumors. It can simulate a more physiological human cancer model in vitro, and hence can translate research from benchside to bedside more efficiently[3]. The area of tumor organoids has gained the attention of many researchers owing to the aforementioned advantages and emerging challenges in the field of tumors [4]. Subsequently, a large number of studies were performed on different aspects of tumor organoids. These studies provided vital information on the variation trend of findings on tumor organoids. This trend helped newcomers and current researchers to choose their research topics. However, analyses of studies on tumor organoids were few.
In this study, a bibliometric analysis was performed by co-word analysis and visualization on tumor organoids. The study described related findings on tumor organoids and their current trend. The hot spots in tumor organoids were analyzed, and the distribution of relevant studies based on tumor type was shown to understand the field of tumor organoids better. This information helped researchers choose research topics, design research projects, and estimate research values.

Materials And Methods

Related studies were obtained from the PubMed database. The advanced search function was used to limit research topics. The detailed search statement was as follows: ((neoplasm [MeSH Major Topic]) AND organoid). This search yielded 1550 relevant study, which were defined as the literature set. All records were preserved in the XML format.

Data extraction and analysis

Data extraction and matrix construction were performed using co-occurrence matrix generation software (BICOMB), which was developed by Professor Lei Cui from China Medical University[5]. The findings relevant to tumor organoids were examined, and the most frequent major Medical Subject Heading (MeSH) terms were counted from the literature set (Table 1). Then, a binary matrix was produced from the literature set using BICOMB. A row was set by identifying studies with their PubMed-Indexed for MEDLINE (PMID), and a column was set as MeSH terms (Table 2). Afterward, gCLUTO 1.0 software (developed by Rasmussen, Newman, and Karypis at the University of Minnesota) was applied[6].
Table 1
High-frequency major topic word from the included publications on organoid (n = 1550).

| No. | Topic word                                  | Frequency n (%) | Cumulative percentage, % |
|-----|---------------------------------------------|-----------------|--------------------------|
| 1   | Skin Neoplasms / pathology                  | 76 1.2745       | 1.2745                   |
| 2   | Organoids                                   | 63 1.0565       | 2.3310                   |
| 3   | Organoids / ultrastructure                  | 58 0.9727       | 3.3037                   |
| 4   | Organoids / pathology                       | 54 0.9056       | 4.2093                   |
| 5   | Breast Neoplasms / pathology                | 50 0.8385       | 5.0478                   |
| 6   | Organoids / drug effects                    | 38 0.6373       | 5.6851                   |
| 7   | Adenocarcinoma / pathology                  | 34 0.5702       | 6.2552                   |
| 8   | Antineoplastic Agents / pharmacology        | 32 0.5366       | 6.7919                   |
| 9   | Nevus / pathology                           | 31 0.5199       | 7.3118                   |
| 10  | Carcinoma / pathology                       | 28 0.4696       | 7.7813                   |
| 11  | Colorectal Neoplasms / genetics             | 28 0.4696       | 8.2509                   |
| 12  | Lung Neoplasms / pathology                  | 28 0.4696       | 8.7204                   |
| 13  | Pancreatic Neoplasms / pathology            | 27 0.4528       | 9.1732                   |
| 14  | Organoids / metabolism                      | 25 0.4193       | 9.5925                   |
| 15  | Models, Biological                          | 25 0.4193       | 10.0117                  |
| 16  | Adenoma / pathology                         | 25 0.4193       | 10.4310                  |
| 17  | Neoplasms / pathology                       | 25 0.4193       | 10.8502                  |
| 18  | Colonic Neoplasms / pathology               | 23 0.3857       | 11.2360                  |
| 19  | Liver Neoplasms / pathology                 | 22 0.3689       | 11.6049                  |
| 20  | Teratoma / pathology                        | 22 0.3689       | 11.9738                  |
| 21  | Nevus, Pigmented / pathology                | 22 0.3689       | 12.3428                  |
| 22  | Thymus Neoplasms / pathology                | 21 0.3522       | 12.6950                  |
| 23  | Breast Neoplasms / metabolism               | 21 0.3522       | 13.0471                  |
| 24  | Carcinoid Tumor / pathology                 | 21 0.3522       | 13.3993                  |
Table 2
High-frequency topic word terms-source articles matrix (localized).

| No. | Topic                                | PubMed Unique Identifiers of source article | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-----|--------------------------------------|---------------------------------------------|---|---|---|---|---|---|---|---|
| 1   | Skin Neoplasms / pathology           | 10048709                                   | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |
| 2   | Organoids                            | 10078927                                   | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |
| 3   | Organoids / ultrastructure           | 10095889                                   | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |
| 4   | Organoids / pathology                |                                             | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |
| ...  | ...                                  |                                             | ... | ... | ... | ... | ... | ... | ... | ... |
| 23  | Breast Neoplasms / metabolism        | 1057351                                    | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |
| 24  | Carcinoid Tumor / pathology          |                                             | 0 | 0 | 0 | 0 | ... | 0 | 0 | 0 |

Strategic coordinates

The co-word analysis was used as a tool to describe the relationship between scientific topics; it helped investigate the differences between local and global environments of each research topic[7]. The co-word matrix composed of high-frequency words was used to calculate the intraclass and interclass link averages using Excel (Table 4).

Results

The search strategy yielded 1550 studies related to tumor organoids. Year-standardized studies and the corresponding organoid search index in Google are shown in Fig. 1. Also, 2773 major topic terms were extracted from the studies on PubMed. As described in the high-frequency term table (Table 1), the frequency number before the 21st word was larger than its original number, and the 22nd and 23rd words shared the same frequency number with the former one. However, after the 24th word, the ordinary number was higher. The terms ranked before the 21st word were related to 736 studies and defined as frequent terms. Then, a co-occurrence analysis of the high-frequency terms was applied. A row was set by identifying studies with their PMID number, and a column was set as MeSH terms (Table 2). In this table, “1” represented the term present and “0” represented the term absent in the reference. These references were distinguished by their PMID number. Finally, a co-word matrix was established (Table 4). This matrix indicated terms present in the selected studies, which showed the association between two topics and their accumulative number (Table 4).

The packed bubble graph was used to visualize based on PubMed so as to describe the hot topic distribution in the field of tumor organoids. In the PubMed database, the larger the weight of the topic, the larger the area, and the more central the module (Fig. 3).
Subsequently, a peak map and a double-clustering heat map were generated, and gCLUTO was used to perform data visualization based on the high-frequency terms in the literature set, which could directly detect the relationship between studies. Moreover, peak, volume, height, and color were all used to describe the associated cluster. According to the literature set, six clusters from 0 to 5 were recognized. Figure 1 shows the heat map of double-clustering visualization, where rows comprise high-frequency major MeSH terms, with the columns of corresponding terms located on the right. The bottom of the heat map showed the PubMed unique identifier of each study. A deep red grid represented a relatively higher frequency of major MeSH terms in the study, while a white grid represented a value closer to zero; negative values were green. The double-clustering matrix visualization showed that 21 highly frequent major MeSH terms were clustered in 6 peaks. In Fig. 1, the hierarchical tree on the left side denotes the relationship between high-frequency MeSH terms, while the hierarchical tree on the top denotes the relationship between studies. The highest expression of MeSH terms in each category was also examined. In Fig. 2, each category is numbered from 0 to 5. Peak, volume, height, and color were all used to provide information about the associated cluster. The peak is the specific area in each topic. The volume is the accumulative article volume in the topic. The more the papers, the higher the height. Moreover, red indicates a low deviation, and blue indicates a high deviation (Fig. 2). The detailed cluster is summarized in Table 3.
| Cluster   | Size | ISim: | Esim: | Descriptive Features | Discriminating Features |
|-----------|------|-------|-------|-----------------------|-------------------------|
| Cluster 0 | 3    | 0.794 | 0.024 | 10048709 10340047 1054896 10078927 | 10048709 10340047 1054896 1026920 |
| Cluster 1 | 3    | 0.533 | 0.025 | 1057351 10399173 10571348 1032517 | 1057351 10399173 10571348 10048709 |
| Cluster 2 | 4    | 0.451 | 0.049 | 1026920 10417695 10463034 10403302 | 1026920 10463034 10417695 10403302 |
| Cluster 3 | 4    | 0.339 | 0.032 | 10323079 1032522 10095889 10483587 | 10323079 1032522 10095889 10483587 |
| Cluster 4 | 5    | 0.335 | 0.047 | 10470114 1032517 10342010 10459830 | 10470114 10342010 10459830 1032517 |
| Cluster 5 | 5    | 0.306 | 0.032 | 1057348 10416596 1057348 10392634 | 1057348 10416596 1057348 10392634 |
In addition, the main groups and the current trend of research in the tumor organoid field was determined by investigating the studies corresponding to each category of clusters. In this way, some clusters could be subdivided or integrated into different topics:

1. Pathology for skin cancer and nevus (cluster 0)
2. Pathology for thymus cancer (cluster 1)
3. Pathology for lung carcinoma (cluster 1)
4. Pancreatic cancer organoid and biology model (cluster 2)
5. Organoid for antineoplastic agents of liver cancer (cluster 3)
6. Organoid for genetic study of colorectal carcinoma (cluster 4)
7. Organoid for metabolism study of breast cancer (cluster 4)
8. Pathology for adenocarcinoma (cluster 5)
9. Pathology for carcinoid tumor (cluster 5)
10. Pathology for teratoma (cluster 5).

Discussion

Organoids can mimic specific aspects of the 3D architecture, cell-type composition, and functionality of real organs while maintaining the advantages of simplified and easily accessible cell culture models[8]. As such, they hold great promise for a range of biological and biomedical applications. However, the related studies often focus on topics such as specific disease modeling, drug discovery, or other aspects; no macroscopic analysis or scientific prediction of tumor organoids has been conducted using bibliometrics[9–12]. In this study, the method of co-word research and double-clustering visualization analysis was used to obtain 6 categories of 10 aspects of tumor organoids as hot spots. According to the co-word matrix, hotspot strategic coordinates were constructed, and an organ or disease distribution map

| No. | Topic Words                               | Skin Neoplasms / pathology | Organoids | ... | Carcinoid Tumor / pathology |
|-----|------------------------------------------|----------------------------|-----------|-----|-----------------------------|
| 1   | Skin Neoplasms / pathology               | 76                         | 2         | ... | 0                           |
| 2   | Organoids                                | 2                          | 63        | ... | 0                           |
| 3   | Organoids / ultrastructure               | 2                          | 0         | ... | 0                           |
| 24  | Carcinoid Tumor / pathology              | 0                          | 0         | ... | 21                          |
was generated to understand the weight of each organ or disease in the tumor organoid field. These results suggested that the tumor model study was an absolute core topic with much interaction with the other categories and good integrality. The organ or disease profile showed that the two most important organs or diseases for tumor organoids were the skin and breast cancer. This distribution might be due to drug effects on skin and breast cancer tested using organoids [13–14]. Several tumors such as carcinoid tumors had few counts, probably because their prognosis depended on location and pathology; the main method was the surgical therapy[15]. The analysis of the extracted literature set showed that the recent tumor organoid research was dominated by disease modeling. In the study of disease modeling, the subcategory analysis indicated that the most popular topics were disease genetic mechanism, drug effect, and metabolism. Although the co-word clustering analysis of high-frequency words is a new method of analysis, a certain degree of bias may exist due to word selection among researchers when writing. Additionally, the quality of studies in the PubMed database is not uniform. Although 1550 study were examined, the dataset may be incomplete due to limitations of intelligence in the retrieval system.

Conclusions

Co-word analysis and co-citation analysis of studies on tumor organoids were performed using various scientometric tools, and 6 categories and 10 hot topics were summarized. The current state of research in this field is polarized. Further, the tumor model is at the absolute core with the most mature research on disease genetic mechanism, drug effect, and metabolism. Future bibliometric analyses should explore the exact function of tumor organoids in different kinds of tumors.

Abbreviations

MeSH: Medical Subject Headings; gCLUTO: Graphical Clustering Toolkit;

Declarations

Authors’ contributions

Conceptualization: CQW, ZY; Data curation: CQW, ZY, LK Formal analysis: CQW, WY; Methodology: CQW, MGY; Writing-original draft: CQW, ZY; All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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