Original Article

Global trends and hotspots in research on organoids between 2011 and 2020: a bibliometric analysis

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Background: There is a lack of effective platforms that can rapidly screen drugs, for patients to achieve precision treatment. Since an organoid simulates the tissue or organ structure and function in vitro, it can be applied to predict the response to therapy, personalized medicine, and drug screening in clinical practice. However, the rapid development of this field meets several challenges. This study aimed to evaluate the current state of the organoid and prioritize future research areas using bibliometric analysis.

Methods: We selected articles and reviewers from the Web of Science database, using the search strategy syntax including "organoid" or "organoids", for the years 2011 to 2020. We conducted a general analysis and a thematic evolution analysis using the bibliometrix R package. Networks connecting productive countries/regions/institutions/authors were generated using VOSviewer. We performed a co-occurrence analysis using VOSviewer, burstness analysis using Citespace, and co-word biclustering analysis and landform map using BICOMB and gCLUTO to identify possible current and future directions and hotspots.

Results: We selected 3,168 publications for our analysis. We found that the number of publications in this field has increased sharply. The greatest contributions to organoid research have been made by the United States (among countries) and the University of Michigan (among institutions), and Hans Clevers is the most influential author. The journals with the highest number of selected articles and citations are *Cancer Research* and *Nature*. We observed the possibility of keyword classification into five clusters. Their trend changed from "methods to build organoids" (e.g., "lgr5+ stem cell" and "3D culture") to "practical applications of organoids" (e.g., "cystic fibrosis" and "Zika virus").

Conclusions: Our study used bibliometric analysis to provide an in-depth understanding of the trends and hotspots of organoid research. The primarily important subject matters are drug screening, disease modeling, personalized medicine, regenerative medicine, and developmental biology. However, this field still faces limitations in the form of lack of reproducibility, low levels of maturity and function, and the absence of appropriate readouts. Therefore, these five significant topics, and possible solutions to limitations (involving bioengineering strategies), might be noteworthy in the future.

Keywords: Bibliometrics; organoid; VOSviewer; CiteSpace; R bibliometrix

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Introduction

Organoids are defined as 3D structures of stem cells that contain different organ-specific cell types. Owing to the wide range of tissue types, the long-term expansion capacity, and the physiological 3D architecture, organoids are a powerful new technology for many biological and clinical applications. Organoids have been used as models of infectious (1,2) and genetic (3,4) diseases, as well as cancer (5,6). Brain organoid technology has been used in developing drugs to prevent or treat Zika infection (7); tumor organoids provide high-throughput chemotherapeutic drug screening platforms (8) and are also conducive to predicting the treatment response for metastatic gastrointestinal cancers (9). The gene correction of cystic fibrosis transmembrane conductance regulator (CFTR) mutation in patients derived organoids using *CRISPR/Cas9* gene editing could repair the CFTR function and treat cystic fibrosis (10). Organoid technology also holds great promise for personalized medicine, as organoids can be used for rapid, *ex vivo* testing of drug responses in diseased tissues or organs of individual patients. In addition, the biological banks can be served as resources for studying cancer biology and drug development. These living organoid biobanks have been established for multiple organs and tumor types, including histologically and genetically characterized tumors and matching normal organoids (11,12). Furthermore, organoids could potentially be investigated for the development of alternative therapy strategies for organ transplantation, such as intestinal and liver organoid transplantation (13,14). In recent years, organoid publications have increased, suggesting that many researchers utilize organoid technology in various fields. However, this rapid expansion of the literature can make it difficult to provide an overall perspective on the field's state and the emerging trends using traditional review methods.

At present, most of the related studies remain scattered, and prove unfavorable to clinical transformation and for serving improved clinical treatment. This requires us to summarize the progress in the existing fields, in order to meet clinical needs. For example, the protocol for culture varies in different systems. An objective summary and analysis of the publications can lead to a standardized organoid culture protocol. Further, summarizing organoid-related publications can contribute to finding out the limitations and the cause of the limitations; for instance, current organoids are not suitable for the screening of immunotherapeutic agents owing to the lack of surrounding stromal cells (15). In addition, the summary and analysis of the publications can help identify possible future solutions to overcome current clinical shortcomings; for example, the combination of organoid and engineering technologies may be the future approach to exploit their potential in clinical applications (16).

The bibliometric analysis is based on statistics and visualization techniques. It is a valuable method to evaluate quantitatively the influence of research papers in a certain period, considering countries, institutions, journals, and research collaborations for any specific topic while measuring developmental research trends and depicting knowledge structures related to a research discipline over time (17,18). Using bibliometrics, investigators can quickly identify the key articles worthy of intensive, careful review among a large number of documents, excavate the frontiers of disciplines, and pinpoint research hotspots. This technique also offers an objective method to determine the influence and importance of disciplines and topics, study the distribution of subject or topic information sources, identify core journals, examine the needs and characteristics of information users, evaluate talents, and visualize data. Bibliometric analyses contain many science mapping tools, which adopt timely, repeatable, and flexible methods to produce a complex interactive visual structure for statistical analyses (19). Traditional reviews cannot accomplish these aims because of the unmanageable manual workload. Moreover, the results of bibliometric analyses are determined by specific indicators rather than the intervention of experts and prior working knowledge or experience in the field. Bibliometric analyses can also be verified by any analyst and repeated. Therefore, bibliometric analyses enable the objective metrological study of organoids. The bibliometrix software package, VOSviewer, CiteSpace BICOMB, and gCLUTO are five frequently used bibliometric tools that allow scientists to evaluate the current state of knowledge in a subject area and identify related hotspots (20,21). Many hotspots on organoids have appeared recently, such as developing novel drugs for tumor patients and predicting patients' responses to individualized treatments using organoids. To the best of our knowledge, this is the first scientometric study that describes organoid research's current and future directions.

We conducted a quantitative analysis of the literature, considering author contributions, country/region/institution/author co-authorship, journal/reference co-citation analysis, document citation analysis, co-occurrence of keywords, thematic evolution, keywords and references

with strong citation burstness, co-word biclustering analysis, and landform map. This study aimed to provide an overview of the field, elucidate the trends in different aspects of organoid research, and point out the limitations of existing research while proposing possible solutions.

Methods

Data source and search strategy

On Oct 4, 2021, we used the Web of Science (WoS) core collection Science Citation Index expanded (SCI-EXPANDED) database (Thomson Reuters, New York, NY, USA) to conduct a literature search and identify all types of documents related to organoids published in the past decade (from 2011 to 2020), with no language restrictions. The search strategy syntax contained "organoid" OR "organoids", searched in topic term. Three authors screened the retrieved literature independently and determined eligibility. Finally, no related documents were excluded. The search identified 3,168 publications (articles and reviews). The full data, including author, title, abstract, keywords, source, language, citation, etc., was downloaded as a BibTeX and txt file from the WoS database. The publications were then processed with the bibliometric tools described below.

Statistical analysis

General analysis and thematic evolution analysis

The general basic characteristics of the retrieved publications, including the country/region, the year of publication, and the authors, were converted and analyzed automatically using the bibliometrix software package in R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel (version Microsoft 365). Journal impact factors were obtained from the 2020 Journal Citation Reports (Clarivate Analytics, Philadelphia, PA, United States). To evaluate the quality of the documents, we used the number of publications and citations in the related fields, the h-index value, and the m-index value. The h-index can be used to evaluate the performance by individual citation analysis of journals/references/citations of documents and co-occurrence of keywords or by groups of scientists working in university departments or research institutes. The m-index facilitates comparing scholars with different academic career lengths (22). In addition, the Bibliometrix software package was used to create a thematic evolution of 10 years, divided into three periods (2011–2014, 2014–2017, and 2017–2020). This enabled the display of changing time-trends of keywords, for those three periods. Furthermore, GraphPad Prism 9.0 was used to conduct nonlinear regression (curve fit) for the trend of the number of publications in this field at each point.

Network analysis

VOSviewer (Version 1.6.16, Leiden University, the Netherlands) was used to analyze organoid research collaboration networks and co-citation networks, as well as to identify research hotspots and future trends. We generated networks connecting productive countries/regions/institutions (if one publication was attributed to authors from more than one country/region, the publication was assigned equally to all participating countries/regions), authors, and co-authors using co-authorship, co-occurrence, citations, and co-citation analysis. Specifically, overlay mapping was conducted to show the time scale of themes in the organoid field. In the visual maps, different colors represented different clusters, and connecting lines indicated collaboration or co-citations. The numbers of documents, citations, and keyword occurrences were represented by circle size, whereas the strength of the links was represented by the thickness of the connecting lines. In the co-occurrence analysis, keywords that occurred more than five times were presented in three visualizations (network, overlay, density visualization) in the co-occurrence networks.

Burstness analysis

CiteSpace (5.8.R5) (http://cluster.cis.drexel.edu/~cchen/citespace/) is a bibliometric tool that utilizes Java to visualize and analyze trends and patterns in scientific documents. We used it to search for keywords and references with strong citation burstness and identify the latest research focus and future directions in organoid research. For burstness analysis visualizations, the parameters of CiteSpace were set as follows: time slicing [2010–2020], years per slice (1 year), and visualization (time zone view). A more detailed description of the software, utilization skills, and options can be found in the CiteSpace manual. The keywords and references surging in the corresponding period suggested the changing trend of possible research focuses.

Co-word biclustering analysis and landform map

The data were imported into BICOMB (23) to construct a keyword-keyword binary matrix (21). The rows and columns represented highly frequent keywords (n>20).

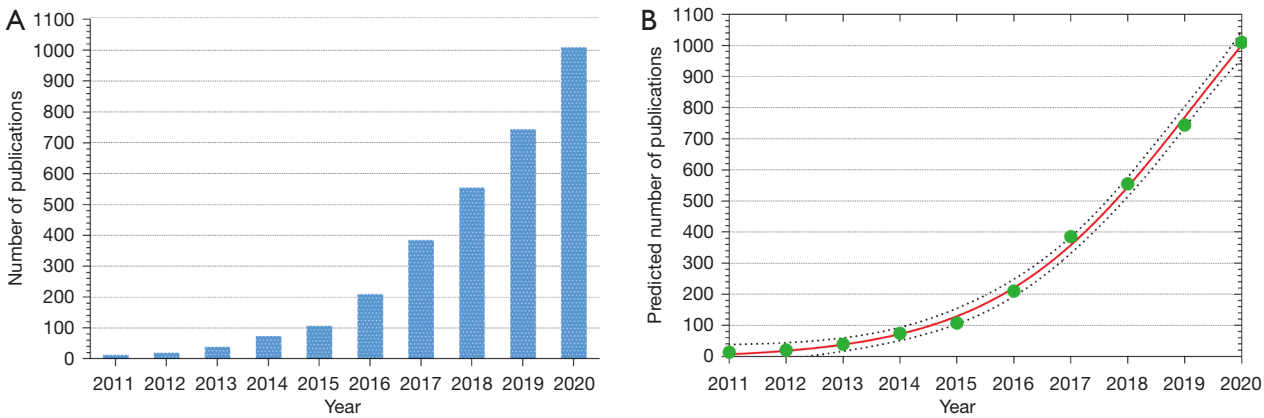


Figure 1 Global trends in the number of publications on organoids. (A) Year-by-year publication output over the past decade. (B) Model fitting curves of growth trends in the number of publications.

Additionally, the gCLUTO software 1.0 was used to perform the clustering analysis; keywords in each cluster may represent a topic. Landform maps and heatmaps were also generated based on the results of the clustering analysis.

Results

Trends in global publications

A total of 3,168 articles related to organoids were retrieved from WoS. Global literature in this field exhibited a strongly increasing trend, going from 13 articles (0.41%) published in 2011 to 1,010 articles (31.9%) published in 2020 (*Figure 1A*). Using logistic regression analysis, we constructed a curve of publications per year, which revealed that this field is currently at the stage of stable growth with respect to global publications output (*Figure 1B*).

Distribution of countries/regions and institutions

To visualize the publication contributions of different countries/regions to organoid-related research, we used R to prepare a world map of publication productivity (*Figure 2A*). A total of 39 countries and regions contributed to publications in this field. The plurality of documents was published by groups based in the United States (1,063, 33.55% of all articles), followed by China (223, 7.04%), the Netherlands (163, 5.15%), Japan (145, 4.58%), and Germany (118, 3.72%) (*Figure 2B*). The highest number of citations emanated from the United States (22,571 citations), followed by the Netherlands (9,995 citations), the United Kingdom (4,659 citations), Japan (4,549 citations), Austria (4,529 citations), and Germany (2,761 citations) (*Figure 2C*).

Next, we conducted a co-authorship analysis of 19 countries/regions that had produced more than 20 publications in this field (*Figure 3A*). The five countries/regions with the highest total link strength among authors were the United States (total link strength =472 times), the Netherlands (227 times), England (200 times), Germany (198 times), and China (157 times).

At the time of our analysis, a total of 2,696 organizations were involved in this field. The University of Michigan had the highest number of publications (290 records, or 10.76% of all articles), followed by the University Medical Center Utrecht (268, 10.76%), the University of Cambridge (196, 7.27%), the University of Pennsylvania (177, 6.57%), and Johns Hopkins University (172, 6.40%).

Finally, we analyzed the co-authorship relationships of 59 institutions with more than 20 publications using viewOS tools. Only one document was excluded (because it was not connected to the others), which suggests that a network of collaboration exists between these 59 institutions (*Figure 3B*). The University Medical Center Utrecht had the greatest total link strength (total link strength =167), followed by the Princess Máxima Center for Pediatric Oncology (total link strength =99), Harvard Medical School (total link strength =96), Universiteit Utrecht (total link strength =87), and the Royal Netherlands Academy of Arts and Sciences (total link strength =79).

Analysis of journals

In all, 3,168 publications were obtained from 696 sources.

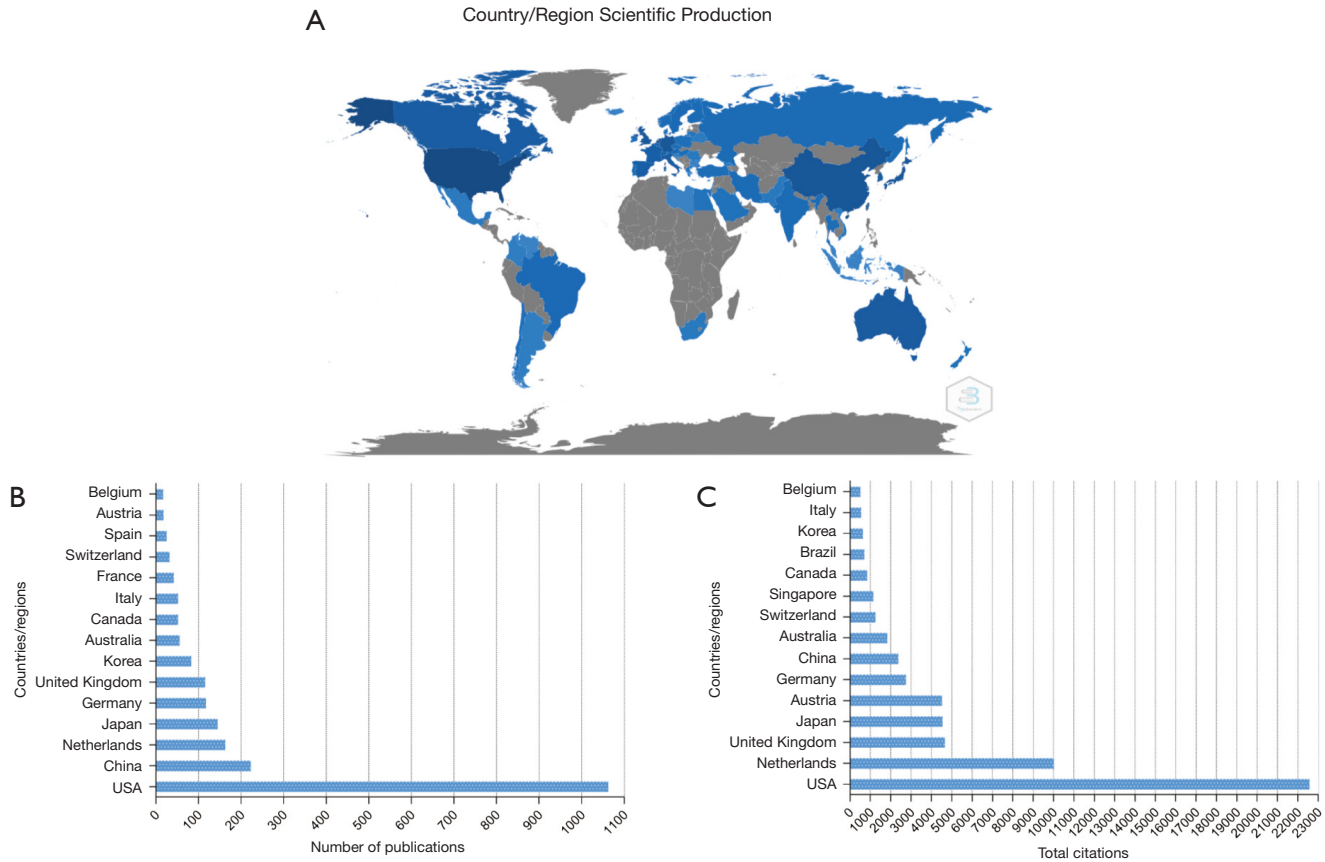


Figure 2 Countries/regions contributing to organoid research. (A) World map showing the contributions of countries/regions in the field of organoid research. Darker shades of blue indicate higher numbers of articles. (B) Top 15 countries/regions with the highest number of publications. (C) Total number of citations of related articles from different countries/regions.

The top 10 most popular journals related to organoids are listed in *Table 1*. *Cancer Research* (175 records, 5.52% of all articles) had the most publications, followed by *Gastroenterology* (114, 3.60%), *Investigative Ophthalmology & Visual Science* (82, 11.79%), *Scientific Reports* (69, 9.91%), and *Cell Stem Cell* (66, 9.48%).

We analyzed a total of 76 journals for publications that were co-cited in more than 200 other publications (*Figure 4*). *Table 1* displays the top 10 journals for citations in this field. *Nature* was cited the most (7,122 citations), followed by *Cell* (4,777 citations), *Cell Stem Cell* (3,864 citations), *Proceedings of the National Academy of Sciences of the United States of America* (*PNAS*) (3,277 citations), and *Science* (2,994 citations).

Analysis of authors

In terms of the number of publications, Hans Clevers is the top author, with 129 related articles (4.07% of all articles), followed by Yaqing Wang (48, 1.52%), Jihoon Kim (34, 1.07%), Jason R. Spence (34, 1.07%), and Marc van de Wetering (33, 1.04%) (*Figure 5A*). In terms of the number of citations in this field, Clevers was again the first (3,021 citations), followed by Madeline A. Lancaster (1,249 citations), Toshiro Sato (952 citations), Juergen A. Knoblich (898 citations), and Edwin Cuppen (801 citations) (*Figure 5B*). Clevers had the highest h-index [47], followed by those from Sato [16], Wang [16], Jeffrey M. Beekman [15], and Spence [15] (*Figure 5C*). The m-index of publications from Clevers (4.273) was also ranked first, followed by those from Kim (2.600), Spence (2.143), Yaqing Wang (2.000), and Li Wang (2.000) (*Figure 5D*). We analyzed a total of 74 authors who were co-authors on more than 10 publications (*Figure 5E*). Excluding 42 authors, who were not connected, 32 demonstrated collaborative links. The five authors with the highest total link strength were Clevers (total link strength

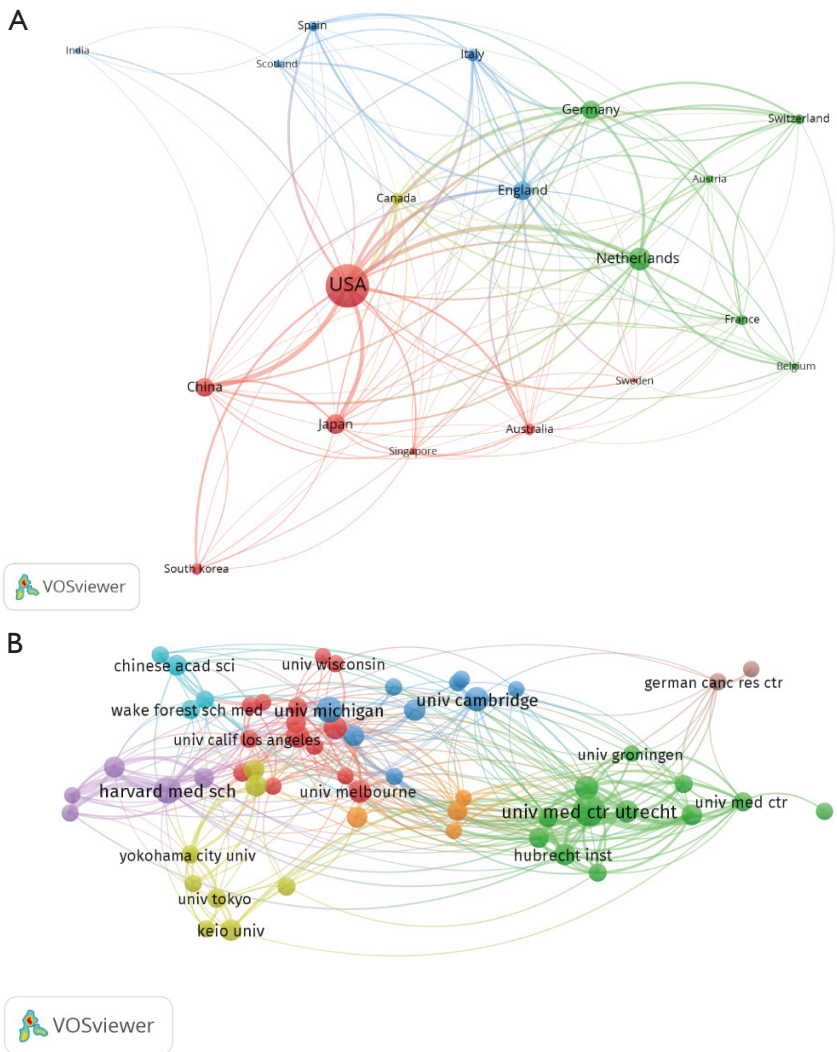


Figure 3 Co-authorship analysis of countries/regions and institutions. (A) Network map of co-authorship between countries/regions with more than 20 publications. (B) Network map of co-authorship between institutions with more than 20 publications. The thickness of the lines indicates the strength of the relationship. USA, The United States of America; Chinese Acad Sci, Chinese Academy of Sciences; Wake Forest sch Med, Wake Forest University School of Medicine; Univ Michigan, University of Michigan; Univ Wisconsin, University of Wisconsin; Univ Calf Los Angeles, University of California, Los Angeles; Harvard Med School, Harvard Medical School; Yokohama City Univ, Yokohama City University; Univ Tokyo, The University of Tokyo; Keio Univ, Keio University; Univ Melbourne, University of Melbourne; Univ Cambridge, University of Cambridge; German Canc Res Ctr, German Cancer Research Center; Univ Groningen, University of Groningen; Univ Med Ctr Utrecht, University Medical Center Utrecht; Hubrecht Inst, Hubrecht Institute; Univ Med Ctr, University Medical Center Utrecht.

=115), Beekman (total link strength =81), Cornelis K. van der Ent (total link strength =75), Johanna F. Dekkers (total link strength =71), and Karin M. de Winter-de Groot (total link strength =63).

Citation and co-citation analyses

Next, the citation analysis revealed that 132 documents had more than 100 citations (*Figure 6A*). *Table 2* lists the ten documents with the highest number of citations.

Table 1 Top ten influential journals and cited journals

Rank	Popular journals	Record (n)	2020 impact factors	2020 JCR partition	Cited journals	Citations (n)	2020 impact factors	2020 JCR partition
1	*Cancer Research*	175	9.727	q1	*Nature*	7,122	42.778	q1
2	*Gastroenterology*	114	17.373	q1	*Cell*	4,777	38.637	q1
3	*Investigative Ophthalmology & Visual Science*	82	3.528	q1	*Cell Stem Cell*	3,864	20.860	q1
4	*Scientific Reports*	69	3.998	q1	*P Natl Acad Sci USA*	3,227	9.412	q1
5	*Cell Stem Cell*	66	20.860	q1	*Science*	2,994	41.845	q1
6	*Pediatric Pulmonology*	60	2.534	q1	*Development*	2,151	5.611	q2
7	*FASEB Journal*	46	4.966	q1	*Nat Med*	2,117	36.13	q1
8	*Jove-Journal of Visualized Experiments*	46	1.163	q3	*PLoS One*	1,742	2.74	q2
9	*Cancer Science*	44	4.966	q1	*Nat Biotechnol*	1,734	36.558	q1
10	*Tissue Engineering Part A*	42	3.496	q2	*Nat Commun*	1,657	12.121	q1

JCR, Journal Citation Reports; P Natl Acad Sci USA, *Proceedings of the National Academy of Sciences of The United States of America*; *Nat Med*, *Nature Medicine*; *Nat Biotechnol*, *Nature Biotechnology*; *Nat Commun*, *Nature Communications*.

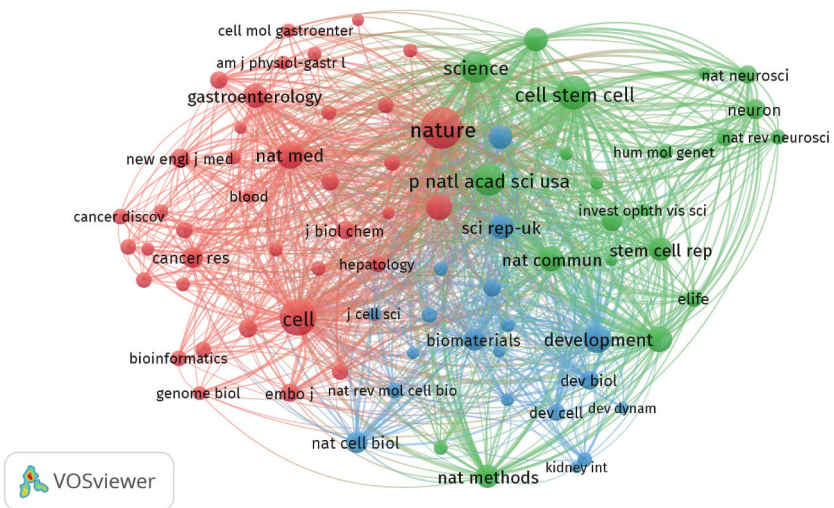


Figure 4 Network map of journals that were co-cited in more than 200 publications. Red: 16 journals, Green: 14 journals, Blue: 4 journals, Yellow: 3 journals. Cell Mol Gastroenter, *Cellular and Molecular Gastroenterology and Hepatology*; Am J Physiol-Gastr L, *American Journal of Physiology-Gastrointestinal and Liver Physiology*; New Engl J Med, *New England Journal of Medicine*; Nat Med, *Nature Medicine*; Cancer Discov, *Cancer Discovery*; Cancer Res, *Cancer Research*; Genome Biol, *Genome Biology*; Embo J, *EMBO Journal*; J Biol Chem, *Journal of Biological Chemistry*; P Natl Acad Sci USA, *Proceedings of the National Academy of Sciences of the United States of America*; Nat Neurisci, *Nature Neuroscience*; Nat Rev Neurosci, *Nature Reviews Neuroscience*; Hun Mol Genet, *Human Molecular Genetics*; Invest Ophth Vis Sci, *Investigative Ophthalmology & Visual Science*; Stem Cell Rep, *Stem Cell Reports*; Nat Commun, *Nature Communications*; Nat Methods, *Nature Methods*; Sci Rep-UK, *Scientific Reports*; J Cell Sci, *Journal of Cell Science*; Nat Rev Mol Cell Bio, *Nature Reviews Molecular Cell Biology*; Dev Biol, *Developmental Biology*; Dev Cell, *Developmental Cell*; Dev Dynam, *Developmental Dynamics*; Nat Cell Biol, *Nature Cell Biology*; Kidney Int, *Kidney International*.

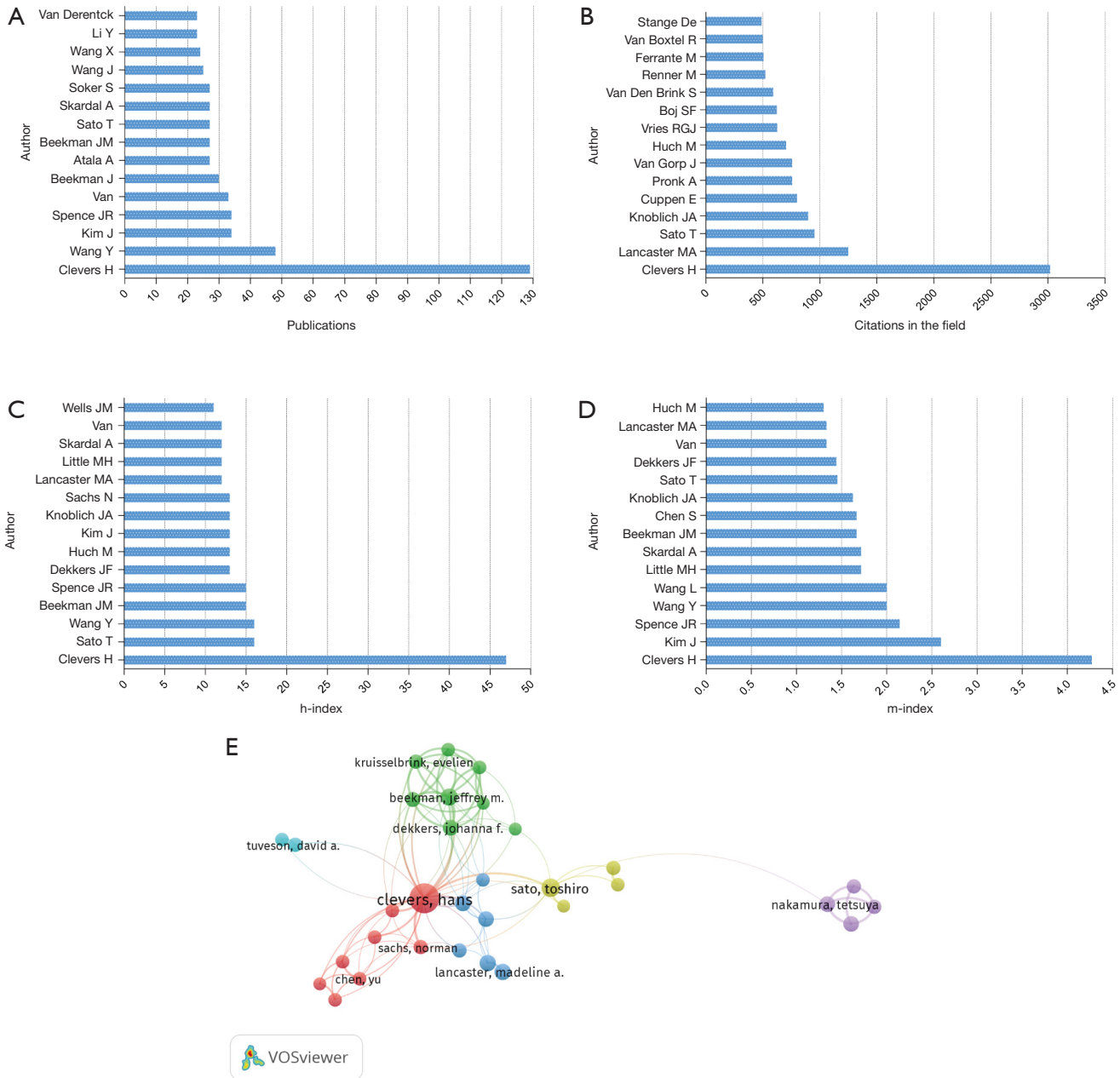


Figure 5 Analysis of authors. (A) Number of publications from different authors. (B) Total number of citations of different authors in the field of organoid research. (C) h-index of publications of different authors. (D) m-index of publications of different authors. (E) Network map of co-authorship between authors with more than 10 publications.

There were 1,872 citations for "*Cerebral organoids model human brain development and microcephaly*" (24), followed by "*Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium*" (25), which was cited 1,463 times. The third-ranked article for the number of citations was "*Organogenesis in a dish: Modeling development and disease using organoid technologies*" (26), which had 1,001 citations.

We analyzed 52 references co-cited in more than 100 citations (*Figure 6B*). *Table 3* lists the top 10 references with the highest number of citations. The five references with the largest number of citations were by Sato *et al.* (33) (2009,

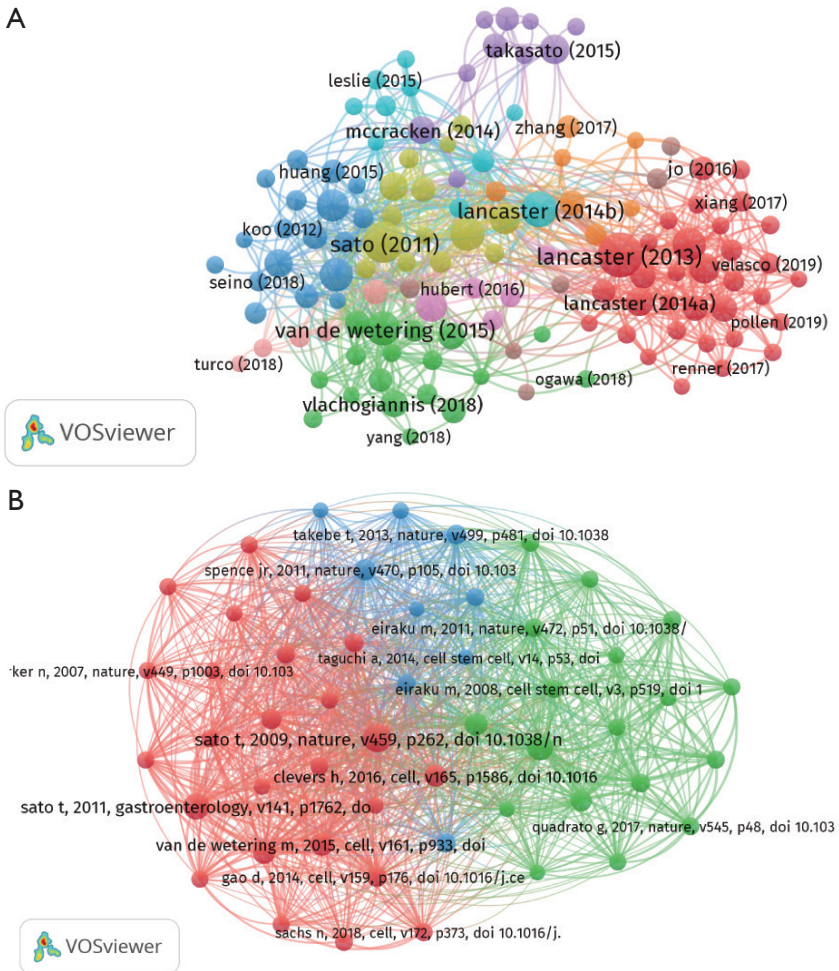


Figure 6 Citation analysis and co-citation analysis. (A) Network map showing the results from citation analysis of articles with more than 100 citations. "2014a" and "2014b" were used to distinguish the two different articles published by Lancaster in 2014; Lancaster (2014a) refers to the article titled "Generation of cerebral organoids from human pluripotent stem cells", while Lancaster (2014b) refers to the other article titled "Organogenesis in a dish: Modeling development and disease using organoid technologies". (B) Network map showing the results from co-citation analysis of articles with more than 100 citations.

Science; 574 citations), Lancaster *et al.* (24) (2013, *Nature*; 453 citations), Sato *et al.* (25) (2011, *Gastroenterology*; 438 citations), van de Wetering *et al.* (29) (2015, *Cell*; 319 citations), and Lancaster, Knoblich (26) (2014, *Science*; 313 citations).

Co-occurrence analysis and thematic evolution analysis

We analyzed 303 keywords that were identified as occurring more than 10 times (*Figure* 7*A*). The colors in the overlay visualizations shown in *Figure* 7*B*,7*C* indicate the average publication year of the identified keywords. Most co-occurring keywords analyzed from 2011 to 2020 that were cited at least 20 times were published after 2018.4, as indicated by the greener and yellower colors on the network map. The density visualization showed the same keywords mapped by frequency of appearance and revealed that the top five co-occurring keywords were "in vitro", "pluripotent stem cells", "differentiation", "stem cells", and "organoids" (*Figure* 7*D*). To better understand the evolution of the research focus, we performed thematic evolution analysis, as shown in *Figure* 7*E*. This analysis was performed by dividing the decade into three periods and visualizing the important keywords for each period and their evolution. Keywords such as "tissue engineering", "lgr5", "mammary gland", "Cohn's disease",

Table 2 Top 10 cited references on organoids

Rank	Title	Authors	Source	Publication, year	Citations (n)
1	Cerebral organoids model human brain development and microcephaly	Lancaster *et al.* (24)	*Nature*	2013	1,872
2	Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium	Sato *et al.* (25)	*Gastroenterology*	2011	1,463
3	Organogenesis in a dish: Modeling development and disease using organoid technologies	Lancaster, Knoblich (26)	*Science*	2014	1,001
4	Modeling development and disease with organoids	Clevers (27)	*Cell*	2016	867
5	Brain-region-specific organoids using mini-bioreactors for modeling ZIKV exposure	Qian *et al.* (28)	*Cell*	2016	865
6	Prospective derivation of a living organoid biobank of colorectal cancer patients	van de Wetering *et al.* (29)	*Cell*	2015	805
7	Organoid models of human and mouse ductal pancreatic cancer	Boj *et al.* (30)	*Cell*	2015	793
8	Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients	Schwank *et al.* (31)	*Cell Stem Cell*	2013	729
9	Organoid cultures derived from patients with advanced prostate cancer	Gao *et al.* (11)	*Nature*	2014	663
10	Zika virus impairs growth in human neurospheres and brain organoids	Garcez *et al.* (32)	*Nature Cell Biology*	2016	604

CFTR, cystic fibrosis transmembrane conductance regulator; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9.

"3D culture", and "inflammatory bowel disease" emerged in organoid research before 2014. New keywords, such as "developmental biology", "patient-derived organoid", "Zika virus", "glioblastoma", and "cystic fibrosis" emerged in 2018–2020, thus creating some new focus vocabulary. The keywords "lgr5" and "3D culture" in the past suggested that the theme at that time was how to build an organoid model. However, the practical and extensive applications of complex organoids are hotspot at present. For example, developmental biology and disease modeling from patient-derived organoids to treat diseases, such as Zika virus (ZIKV), glioblastoma, and cystic fibrosis, have become new hot topics in recent years.

Burstness analysis of keywords and references

The burst detection allows researchers to identify publications and keywords that have received particular attention from related scientific communities during a certain period. Using CiteSpace to conduct the burstness analysis of keywords, we identified 120 keywords with strong citation burstness, indicating a trend of popular keywords from 2011–2020 (*Figure 8A*). The red rectangle on the right side of *Figure 8A* indicates a surge in the number of citations of the keyword at this stage. The most recent citation bursts of keywords, such as developmental biology, microenvironment, and xenograft, represent the most recent research focus areas in the field. In addition, our burst detection analysis also identified 90 articles with strong citation burstness (*Figure 8B*). The most recent citation bursts of publications were from eight articles whose bursts ended in 2020; among them, publications with relatively strong burstness were published in *Nature Protocols*, *Nature Communications*, *Nature*, *Development*, *Gut*, *Mucosal Immunology*, and *Assay and Drug Development Technologies*.

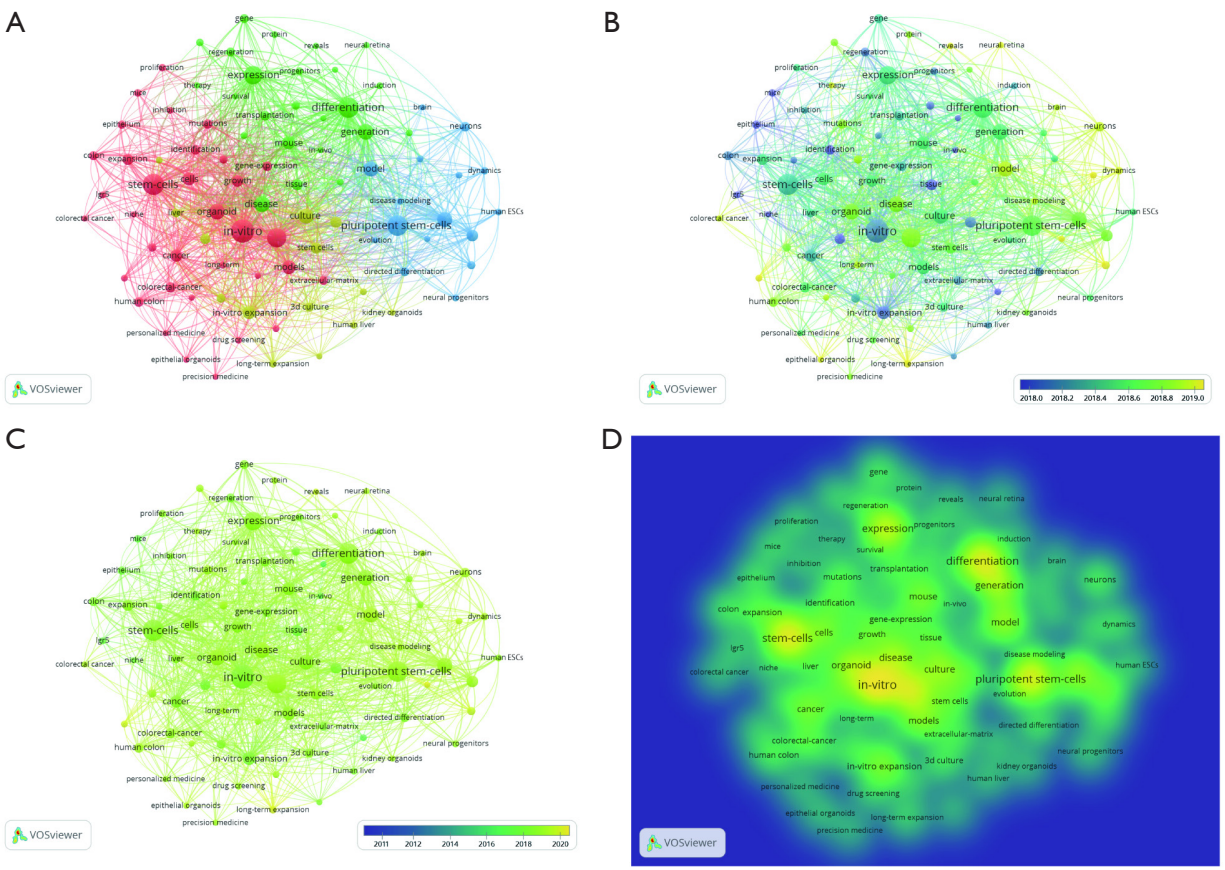
Co-word biclustering analysis and landform map

BICOMB and gCLUTO were performed to identify the correlation degree of each keyword and classify them into five clusters. The connections within clusters were also

Table 3 Top 10 co-cited documents on organoids

Rank	Title	Authors	Source	Publication, year	Citations (n)
1	Single Lgr5 stem cells build crypt-villus structures *in vitro* without a mesenchymal niche	Sato *et al.* (33)	*Nature*	2009	574
2	Cerebral organoids model human brain development and microcephaly	Lancaster *et al.* (24)	*Nature*	2013	453
3	Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium	Sato *et al.* (25)	*Gastroenterology*	2011	438
4	Prospective derivation of a living organoid biobank of colorectal cancer patients	van de Wetering *et al.* (29)	*Cell*	2015	319
5	Organogenesis in a dish: modeling development and disease using organoid technologies	Lancaster, Knoblich (26)	*Science*	2014	313
6	Modeling Development and Disease with Organoids	Clevers (27)	*Cell*	2016	293
7	Organoid models of human and mouse ductal pancreatic cancer	Boj *et al.* (30)	*Cell*	2015	268
8	Directed differentiation of human pluripotent stem cells into intestinal tissue *in vitro*	Spence *et al.* (34)	*Nature*	2011	249
9	Organoid cultures derived from patients with advanced prostate cancer	Gao *et al.* (11)	*Cell*	2014	243
10	Vascularized and functional human liver from an iPSC-derived organ bud transplant	Takebe *et al.* (35)	*Nature*	2013	216

Lgr5, leucine rich repeat containing g protein-coupled receptor 5; iPSC, induced pluripotent stem cell.



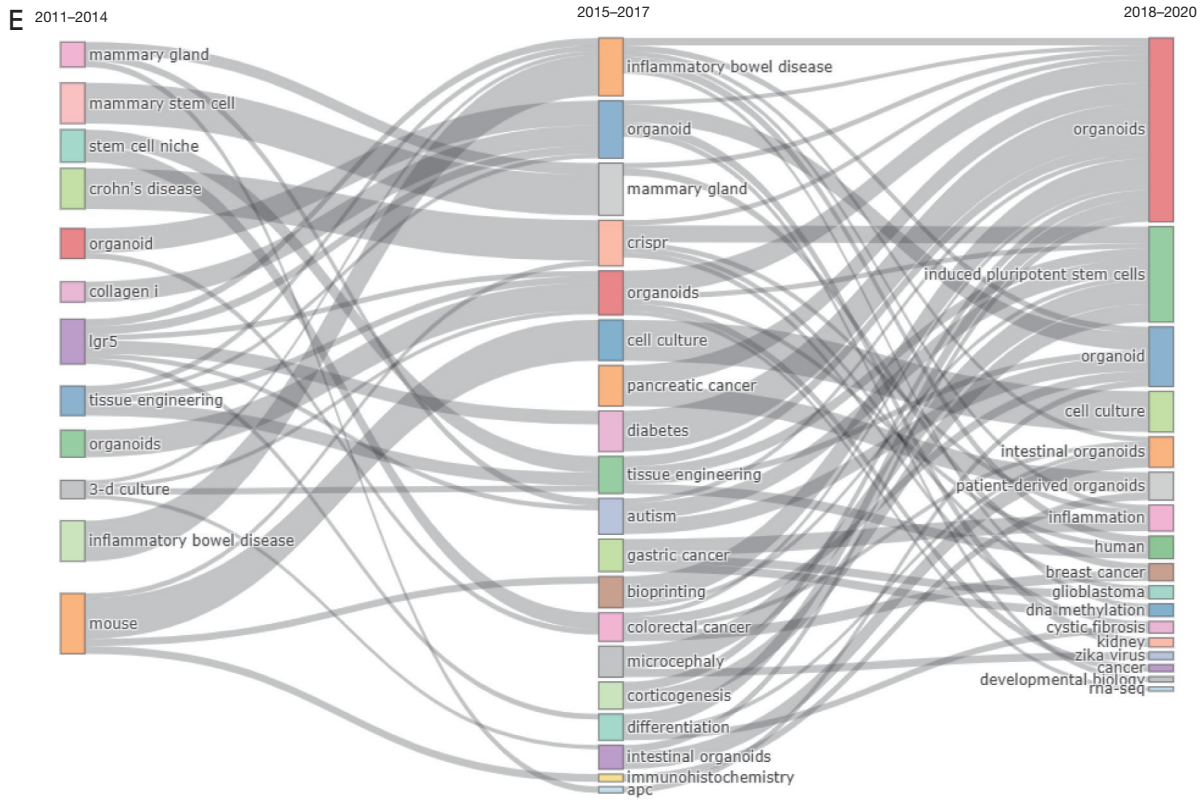


Figure 7 Co-occurrence analysis of keywords. (A) Mapping of keywords used in different articles. (B) Distribution of keywords according to the number of articles in the same publication year. The color spectrum indicates publication dates ranging from 2018.0 (blue) to 2019.0 (yellow). (C) Distribution of keywords according to the number of articles in the same publication year. The color spectrum indicates publication dates ranging from 2011 (blue) to 2020 (yellow). (D) Distribution of keywords according to the mean frequency of appearance. Keywords in yellow had the highest frequency of appearance. (E) Evolution of themes from 2011 to 2020. human ESCs, human embryonic stem cells; Lgr5, Leucine Rich Repeat Containing G Protein-Coupled Receptor 5; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; APC, Antigen-presenting cells; RNA-seq, RNA-sequencing.

displayed by dendrograms on the axes. The darker the red, the higher the degree of correlation. Interestingly, each cluster could be grouped into a theme. Cluster 0 represented precise treatment; cluster 1 represented disease modeling and drug screening; cluster 2 represented methods to build organoid systems; cluster 3 represented developmental biology; cluster 4 represented tissue engineering and bioengineering (*Figure 9A*,*9B*). A 3D landform map was generated to reveal the inter-cluster standard deviation (*Figure 9C*). The curve of each mountain peak was a Gaussian curve, which approximately reflected the distribution of the data in the associated cluster. Position and height reflected the inter-cluster similarity, whereas the volume reflected the number of terms within the cluster. The most meaningful information was the color of the peak, which revealed the inter-cluster standard deviation; red indicated low deviation, while blue denoted high variance.

Discussion

Using a group of research-based articles on organoids retrieved from the WoS database, published between 2011 and 2020, we performed bibliometric analyses combined with network visualizations to obtain a comprehensive view of the current research trends concerning organoids and provide a reference for researchers in this field. To this end, we analyzed the contributions of countries or regions, organizations, journals, and authors to this emerging field and predicted hot topics that warranted further research. Since 2011, the annual number of publications related to organoid research has increased sharply, suggesting that the

A **Top 102 Keywords with the Strongest Citation Bursts**

Keywords	Year	Strength	Begin	End	2011 - 2020
adipose tissue	2011	7.64	2011	2012	
small intestine	2011	7.59	2011	2012	
epithelial cell	2011	5.06	2011	2015	
inhibition	2011	4.79	2011	2012	
branching morphogenesis	2011	2.17	2011	2012	
proliferation	2011	2.04	2011	2012	
endothelial cell	2011	1.25	2011	2012	
lgr5	2011	20.96	2012	2015	
colon	2011	12.85	2012	2015	
mouse small intestine	2011	12.6	2012	2013	
self renewal	2011	10.69	2012	2016	
epithelium	2011	9.03	2012	2017	
in vivo	2011	6.25	2012	2016	
crypt-organoid	2011	6.11	2012	2014	
proximal-tubule	2011	6.11	2012	2014	
organoid culture	2011	5.74	2012	2013	
origin	2011	4.27	2012	2013	
extracellular matrix	2011	1.98	2012	2013	
animal model	2011	0.93	2012	2013	
embryonic stem cell	2011	8.53	2013	2014	
wnt/beta catenin	2011	7.25	2013	2014	
cancer biology	2011	6.82	2013	2014	
tissue engineering	2011	5.88	2013	2015	
definitive endoderm	2011	4.77	2013	2015	
homeostasis	2011	3.15	2013	2014	
basement membrane	2011	2.98	2013	2014	
intestinal stem cell	2011	2.42	2013	2015	
transplantation	2011	2.41	2013	2016	
regeneration	2011	1.53	2013	2014	
identification	2011	0.69	2013	2014	
in vitro expansion	2011	8.48	2014	2017	
crypt	2011	4.73	2014	2015	
tumor suppressor	2011	4.71	2014	2015	
beta catenin	2011	3.35	2014	2015	
directed differentiation	2011	2.61	2014	2016	
tumorigenesis	2011	2.52	2014	2015	
wnt	2011	2.33	2014	2015	
human esc	2011	2.26	2014	2016	
fate	2011	2.11	2014	2015	
hepatocyte	2011	1.92	2014	2015	
marker	2011	1.74	2014	2015	
intermediate mesoderm	2011	8.74	2015	2017	
basal cell	2011	8.55	2015	2017	
mesenchymal transition	2011	6.47	2015	2016	
adenoma	2011	5.7	2015	2017	
3 dimensional culture	2011	5.68	2015	2017	
population	2011	5.62	2015	2016	
progenitor cell	2011	5.19	2015	2017	
phenotype	2011	5.08	2015	2016	
epithelial mesenchymal transition	2011	4.38	2015	2016	
p53	2011	3.23	2015	2016	
cftr	2011	2.62	2015	2016	
feature	2011	2.24	2015	2016	
nf kappa b	2011	2	2015	2016	
paneth cell	2011	2	2015	2016	
biology	2011	1.52	2015	2017	
transcription	2011	0.84	2015	2016	
cell culture	2011	0.53	2015	2016	
outer subventricular zone	2011	4.94	2016	2017	
cystic fibrosis	2011	4.26	2016	2018	
kidney development	2011	4.14	2016	2017	
human brain	2011	3.79	2016	2018	
cerebralorganoid	2011	3.42	2016	2017	
functional human liver	2011	3.34	2016	2018	
morphogenesis	2011	3.33	2016	2018	
nephron progenitor	2011	3.21	2016	2017	
niche	2011	2.48	2016	2017	
mice	2011	6.11	2017	2018	
prostate cancer	2011	5.76	2017	2018	
stem cell niche	2011	5.44	2017	2018	
neural progenitor	2011	5.16	2017	2020	
stem/progenitor cell	2011	4.89	2017	2020	
target	2011	4.11	2017	2020	
growth factor	2011	3.58	2017	2018	
brain development	2011	3.31	2017	2018	
zika virus	2011	2.99	2017	2018	
cortical neuron	2011	1.87	2017	2018	
infection	2011	1.86	2017	2018	
dna	2011	1.55	2017	2018	
hydrogel	2011	1.54	2017	2018	
colon cancer	2011	1.49	2017	2018	
gene therapy	2011	0.96	2017	2018	
replication	2011	0.42	2017	2018	
organogenesis	2011	5.86	2018	2020	
developmental biology	2011	4.14	2018	2020	
derivation	2011	4.14	2018	2020	
maturation	2011	3.4	2018	2020	
disorder	2011	3.25	2018	2020	
bone marrow	2011	3.09	2018	2020	
neurogenesis	2011	3.07	2018	2020	
cisplatin	2011	2.41	2018	2020	
microenvironment	2011	2.38	2018	2020	
angiogenesis	2011	2.04	2018	2020	
neural stem cell	2011	1.68	2018	2020	
adult stem cell	2011	1.36	2018	2020	
xenograft	2011	1.35	2018	2020	
human ips cell	2011	1.35	2018	2020	
sensitivity	2011	1.34	2018	2020	
cardiomyocyte	2011	1	2018	2020	
beta cell	2011	0.99	2018	2020	
c myc	2011	0.67	2018	2020	
chemotherapy	2011	0.61	2018	2020	

B **Top 90 References with the Strongest Citation Bursts**

References	Year	Strength	Begin	End	2011 - 2020
Sato T, 2011, NATURE, V469, P415, DOI 10.1038/nature09637, DOI	2011	23.87	2011	2016	
Sato T, 2011, GASTROENTEROLOGY, V141, P1762, DOI 10.1053/j.gastro.2011.07.050, DOI	2011	44.49	2012	2016	
Spence JR, 2011, NATURE, V470, P105, DOI 10.1038/nature09691, DOI	2011	29.8	2012	2016	
Sato T, 2009, NATURE, V459, P262, DOI 10.1038/nature07935, DOI	2009	20.84	2012	2014	
Barker N, 2010, CELL STEM CELL, V6, P25, DOI 10.1016/j.stem.2009.11.013, DOI	2010	15.54	2012	2015	
McCracken KW, 2011, NAT PROTOC, V6, P1920, DOI 10.1038/nprot.2011.410, DOI	2011	11.66	2012	2016	
Ootani A, 2009, NAT MED, V15, P1, DOI 10.1038/nm.1951, DOI	2009	4.03	2012	2014	
Akcay A, 2009, MEDIAT INFLAMM, V2009, P0, DOI 10.1155/2009/137072, DOI	2009	2.68	2012	2014	
Yui SR, 2012, NAT MED, V18, P618, DOI 10.1038/nm.2695, DOI	2012	28.67	2013	2017	
Huch M, 2013, NATURE, V494, P247, DOI 10.1038/nature11826, DOI	2013	28.34	2013	2018	
Dekkers JF, 2013, NAT MED, V19, P939, DOI 10.1038/nm.3201, DOI	2013	26.35	2013	2018	
Koo BK, 2012, NAT METHODS, V9, P81	2012	16.21	2013	2017	
Jung P, 2011, NAT MED, V17, P1225, DOI 10.1038/nm.2470, DOI	2011	14.66	2013	2016	
Finkbeiner SR, 2012, MBIO, V3, P0, DOI 10.1128/mBio.00159-12, DOI	2012	9.53	2013	2017	
de Lau W, 2011, NATURE, V476, P293, DOI 10.1038/nature10337, DOI	2011	9.38	2013	2016	
Mariani J, 2012, P NATL ACAD SCI USA, V109, P12770, DOI 10.1073/pnas.1202944109, DOI	2012	8.57	2013	2017	
Clancy JP, 2012, THORAX, V67, P12, DOI 10.1136/thoraxjnl-2011-200393, DOI	2012	3.51	2013	2016	
Ramsey BW, 2011, NEW ENGL J MED, V365, P1663, DOI 10.1056/NEJMoa1105185, DOI	2011	3.51	2013	2016	
Flume PA, 2012, CHEST, V142, P718, DOI 10.1378/chest.11-2672, DOI	2012	2.93	2013	2016	
Howell JC, 2011, REGEN MED, V6, P743	2011	2.6	2013	2015	
Lancaster MA, 2013, NATURE, V501, P373, DOI 10.1038/nature12517, DOI	2013	61.71	2014	2018	
Takebe T, 2013, NATURE, V499, P481, DOI 10.1038/nature12271, DOI	2013	31.15	2014	2018	
Schwank G, 2013, CELL STEM CELL, V13, P653, DOI 10.1016/j.stem.2013.11.002, DOI	2013	26.43	2014	2018	
Huch M, 2013, EMBO J, V32, P2708, DOI 10.1038/emboj.2013.204, DOI	2013	22.73	2014	2018	
Sato T, 2013, SCIENCE, V340, P1190, DOI 10.1126/science.1234852, DOI	2013	21.39	2014	2018	
Nakano T, 2012, CELL STEM CELL, V10, P771, DOI 10.1016/j.stem.2012.05.009, DOI	2012	19.77	2014	2017	
Eiraku M, 2011, NATURE, V472, P51, DOI 10.1038/nature09941, DOI	2011	15.98	2014	2016	
Takasato M, 2014, NAT CELL BIOL, V16, P118, DOI 10.1038/ncb2894, DOI	2014	14.8	2014	2017	
Xia Y, 2013, NAT CELL BIOL, V15, P1507, DOI 10.1038/ncb2872, DOI	2013	12.04	2014	2017	
Koehler KR, 2013, NATURE, V500, P217, DOI 10.1038/nature12298, DOI	2013	9.75	2014	2017	
Stange DE, 2013, CELL, V155, P357, DOI 10.1016/j.cell.2013.09.008, DOI	2013	9.63	2014	2017	
Suga H, 2011, NATURE, V480, P57, DOI 10.1038/nature10637, DOI	2011	8.87	2014	2016	
Greggio C, 2013, DEVELOPMENT, V140, P4452, DOI 10.1242/dev.096628, DOI	2013	8.78	2014	2017	
Taguchi A, 2014, CELL STEM CELL, V14, P53, DOI 10.1016/j.stem.2013.11.010, DOI	2014	6.75	2014	2017	
Hynds RE, 2013, STEM CELLS, V31, P417, DOI 10.1002/stem.1290, DOI	2013	6.26	2014	2017	
Ranga A, 2014, ADV DRUG DELIVER REV, V69, P19, DOI 10.1016/j.addr.2014.02.006, DOI	2014	6	2014	2018	
Clevers H, 2013, CELL, V154, P274, DOI 10.1016/j.cell.2013.07.004, DOI	2013	5.66	2014	2018	
Onuma K, 2013, P NATL ACAD SCI USA, V110, P11127, DOI 10.1073/pnas.1221926110, DOI	2013	5.33	2014	2018	
Nasu M, 2012, PLOS ONE, V7, P0, DOI 10.1371/journal.pone.0053024, DOI	2012	4.81	2014	2017	
Antonica F, 2012, NATURE, V491, P66, DOI 10.1038/nature11525, DOI	2012	4.73	2014	2016	
Barretina J, 2012, NATURE, V483, P603, DOI 10.1038/nature11003, DOI	2012	4.33	2014	2017	
Longmire TA, 2012, CELL STEM CELL, V10, P398, DOI 10.1016/j.stem.2012.01.019, DOI	2012	4.33	2014	2017	
Stelzner M, 2012, AM J PHYSIOL-GASTR L, V302, P0, DOI 10.1152/ajpgi.00493.2011, DOI	2012	4.14	2014	2016	
Liu XF, 2012, AM J PATHOL, V180, P599, DOI 10.1016/j.ajpath.2011.10.036, DOI	2012	3.55	2014	2016	
Katano T, 2013, BIOCHEM BIOPH RES CO, V432, P558, DOI 10.1016/j.bbrc.2013.02.051, DOI	2013	2.95	2014	2016	
Cao L, 2011, DIFFERENTIATION, V81, P1, DOI 10.1016/j.diff.2010.09.182, DOI	2011	2.95	2014	2016	
McCracken KW, 2014, NATURE, V516, P400, DOI 10.1038/nature13863, DOI	2014	20.6	2015	2017	
Gao D, 2014, CELL, V159, P176, DOI 10.1016/j.cell.2014.08.016, DOI	2014	14.67	2015	2018	
Watson CL, 2014, NAT MED, V20, P1310, DOI 10.1038/nm.3737, DOI	2014	12.18	2015	2018	
Karthaus WR, 2014, CELL, V159, P163, DOI 10.1016/j.cell.2014.08.017, DOI	2014	11.12	2015	2017	
Yin XL, 2014, NAT METHODS, V11, P106, DOI 10.1038/nmeth.2737, DOI	2014	9.73	2015	2018	
Li XN, 2014, NAT MED, V20, P769, DOI 10.1038/nm.3585, DOI	2014	8.35	2015	2018	
Lam AQ, 2014, J AM SOC NEPHROL, V25, P1211, DOI 10.1681/ASN.2013080831, DOI	2014	7.43	2015	2017	
Mae SI, 2013, NAT COMMUN, V4, P0, DOI 10.1038/ncomms2378, DOI	2013	7.43	2015	2017	
Schumacher MA, 2015, J PHYSIOL-LONDON, V593, P1809, DOI 10.1113/jphysiol.2014.283028, DOI	2015	5.94	2015	2017	
Mali P, 2013, SCIENCE, V339, P823, DOI 10.1126/science.1232033, DOI	2013	5.44	2015	2017	
Farin HF, 2012, GASTROENTEROLOGY, V143, P1518, DOI 10.1053/j.gastro.2012.08.031, DOI	2012	5.44	2015	2017	
Matano M, 2015, NAT MED, V21, P256, DOI 10.1038/nm.3802, DOI	2015	4.81	2015	2017	
Assawachananont J, 2014, STEM CELL REP, V2, P662, DOI 10.1016/j.stemcr.2014.03.011, DOI	2014	4.51	2015	2018	
Lee JH, 2014, CELL, V156, P440, DOI 10.1016/j.cell.2013.12.039, DOI	2014	4.06	2015	2017	
Song JJ, 2013, NAT MED, V19, P646, DOI 10.1038/nm.3154, DOI	2013	3.96	2015	2017	
Barker N, 2014, NAT REV MOL CELL BIO, V15, P19, DOI 10.1038/nrm3721, DOI	2014	3.26	2015	2017	
Freedman BS, 2013, J AM SOC NEPHROL, V24, P1571, DOI 10.1681/ASN.2012111089, DOI	2013	2.97	2015	2017	
Buczacki SJA, 2013, NATURE, V495, P65, DOI 10.1038/nature11965, DOI	2013	2.43	2015	2018	
Lancaster MA, 2014, SCIENCE, V345, P0, DOI 10.1126/science.1247125, DOI	2014	20.72	2016	2018	
Kadoshima T, 2013, P NATL ACAD SCI USA, V110, P20284, DOI 10.1073/pnas.1315710110, DOI	2013	18.34	2016	2018	
Fordham RP, 2013, CELL STEM CELL, V13, P734, DOI 10.1016/j.stem.2013.09.015, DOI	2013	10.78	2016	2018	
Nowakowski TJ, 2016, CELL STEM CELL, V18, P591, DOI 10.1016/j.stem.2016.03.012, DOI	2016	7.06	2016	2018	
Cong L, 2013, SCIENCE, V339, P819, DOI 10.1126/science.1231143, DOI	2013	6.69	2016	2018	
Chua CW, 2014, NAT CELL BIOL, V16, P951, DOI 10.1038/ncb3047, DOI	2014	5.84	2016	2018	
Pagliuca FW, 2014, CELL, V159, P428, DOI 10.1016/j.cell.2014.09.040, DOI	2014	5.57	2016	2018	
Barkauskas CE, 2013, J CLIN INVEST, V123, P3025, DOI 10.1172/JCI68782, DOI	2013	4.83	2016	2018	
Nanduri LSY, 2014, STEM CELL REP, V3, P957, DOI 10.1016/j.stemcr.2014.09.015, DOI	2014	4.83	2016	2018	
Sachs N, 2014, CURR OPIN GENET DEV, V24, P68, DOI 10.1016/j.gde.2013.11.012, DOI	2014	4.68	2016	2018	
Bhatia SN, 2014, NAT BIOTECHNOL, V32, P760, DOI 10.1038/nbt.2989, DOI	2014	4.53	2016	2018	
Fukuda M, 2014, GENE DEV, V28, P1752, DOI 10.1101/gad.245233.114, DOI	2014	4.25	2016	2018	
Grun D, 2015, NATURE, V525, P251, DOI 10.1038/nature14966, DOI	2015	4.2	2016	2018	
DeWard AD, 2014, CELL REP, V9, P701, DOI 10.1016/j.celrep.2014.09.027, DOI	2014	4.06	2016	2018	
Grabinger T, 2014, CELL DEATH DIS, V5, P0, DOI 10.1038/cddis.2014.183, DOI	2014	4.01	2016	2018	
Koehler KR, 2014, NAT PROTOC, V9, P1229, DOI 10.1038/nprot.2014.100, DOI	2014	3.71	2016	2018	
Wang X, 2015, NATURE, V522, P173, DOI 10.1038/nature14484, DOI	2015	3.34	2016	2018	
Forster R, 2014, STEM CELL REP, V2, P838, DOI 10.1016/j.stemcr.2014.05.001, DOI	2014	3.34	2016	2018	
Lancaster MA, 2014, NAT PROTOC, V9, P2329, DOI 10.1038/nprot.2014.158, DOI	2014	15.65	2017	2020	
Zhong XF, 2014, NAT COMMUN, V5, P0, DOI 10.1038/ncomms5047, DOI	2014	7.64	2017	2020	
Choi SH, 2014, NATURE, V515, P274, DOI 10.1038/nature13800, DOI	2014	4.2	2017	2020	
Takebe T, 2014, NAT PROTOC, V9, P396, DOI 10.1038/nprot.2014.020, DOI	2014	4.01	2017	2020	
Wells JM, 2014, DEVELOPMENT, V141, P752, DOI 10.1242/dev.097386, DOI	2014	4.01	2017	2020	
Schlaermann P, 2016, GUT, V65, P202, DOI 10.1136/gutjnl-2014-307949, DOI	2016	4.01	2017	2020	
Moon C, 2014, MUCOSAL IMMUNOL, V7, P818, DOI 10.1038/mi.2013.98, DOI	2014	3.24	2017	2020	
Edmondson R, 2014, ASSAY DRUG DEV TECHN, V12, P207, DOI 10.1089/adt.2014.573, DOI	2014	2.67	2017	2020	

Figure 8 Keywords (A) and references (B) with strong citation burstness related to organoid research. human esc, human embryonic stem cell; lgr5, Leucine Rich Repeat Containing G Protein-Coupled Receptor 5; p53, protein 53; cftr, cystic fibrosis transmembrane conductance regulator; nf kappa b, nuclear factor kappa-B; human ips cell, human induced pluripotent stem cell; c myc, cellular-myelocytomatosis viral oncogene.

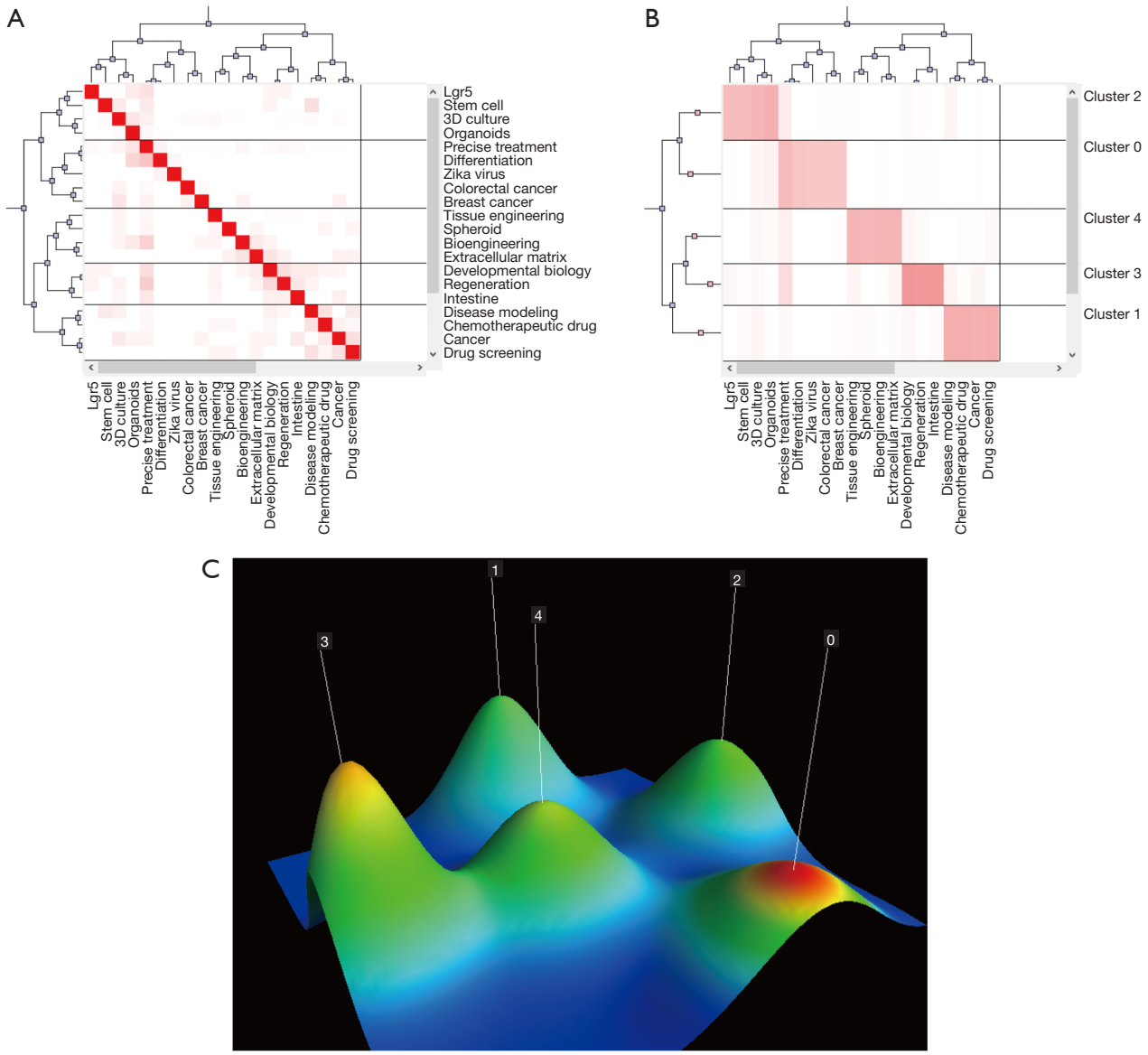


Figure 9 Co-word biclustering analysis and Landform Map. (A) Visualization heatmap of highly frequent keywords matrix related to the correlation between all keywords. The depth of red indicates the correlation degree of the keywords. (B) All keywords are classified into five clusters (0–4). (C) Mountain visualization map of highly frequent keywords related to organoid. The most meaningful information is the color of the peak, which reveals the inter-cluster standard deviation. Red indicates low variation, whereas blue denotes high dispersion. Lgr5, leucine rich repeat containing g protein-coupled receptor 5.

enormous potential inherent in organoid technology may have inspired researchers to make increasing use of this exciting technique. Indeed, we believe that organoids hold the potential to revolutionize disease research profoundly.

Our analyses revealed that the USA had the highest number of publications and citations and ranked first in the national co-author analysis; hence, the USA is the clear leader in this field, with a significant impact and the greatest collaborative activity with other countries/regions in organoid research. The number of studies on organoids conducted in China (223, 7.04%), the Netherlands (163, 5.15%), Japan (145, 4.58%), and Germany (118, 3.72%) increased significantly over the years, accounting for 20.49% of all included studies; thus, these five countries

are particularly influential in the field of organoid research. Among the top 15 most influential countries/regions in organoid research, eight were European, which suggests that European research capacity is relatively strong. China ranks fourth, sixth, and fifth in the total number of papers published, the total number of citations, and cooperation with other countries/regions, respectively. The University of Michigan is the most productive in terms of organoid research, and the University Medical Center Utrecht ranks first in the co-authorship analysis, which suggests that it cooperates closely with other organizations.

Cancer Research has published the highest number of organoid-related articles among all journals in the field of organoid research, while *Nature* is the most co-cited journal in the field, with 7,122 citations. In addition, the top journals *Cell* and *Science* were ranked second and fifth in the co-cited list, respectively. *Cell Stem Cell* was the only journal in the top 10 for both productiveness and co-citation.

Hans Clevers of the University Medical Center Utrecht in the Netherlands is an outstanding scientist in the field of organoid research. He ranks first in the number of articles published, and his articles have been cited over 3,000 times, which is more than twice as many citations as the next author on the list; hence, he ranks first among authors in terms of h-index, m-index, and co-authorship analysis results. Clevers' h-index and m-index results were 47 and 4.273, respectively, which indicates that this author has made a major contribution to the literature and that he is a pioneer and key author in organoid research.

Influential studies

A publication's number of citations often reflects its academic influence. We analyzed the 10 most frequently cited articles in the field of organoid research, demonstrating significant advances in organoid research, using the VOSviewer tool. The study with the highest number of citations (n=1,872) was published in *Nature* in 2013 (24). It demonstrated a novel approach to studying human neurodevelopmental processes by using human pluripotent stem cells to construct and culture cerebral organoids *in vitro*. This method recapitulates the fundamental mechanisms of mammalian neurodevelopment and displays the characteristics of human brain development. In addition, these authors modeled microcephaly using these cerebral organoids, which suggested that organoids could be used to provide novel insights into the pathogenesis of neurological diseases. In 2011, Sato *et al.* (25) published an article in *Gastroenterology*, which ranked second (n=1,463) in terms of the number of citations. The authors reported that they used the replicative potential of adult stem cells to construct organoids that could be used to study infected, inflammatory, or neoplastic tissues from the human gastrointestinal tract. A review by Lancaster and Knoblich, published in *Science* in 2014, was cited 1,001 times, ranking third in the top 10 cited articles (26). This article summarized the rapidly growing field of organoids and outlined the future potential of organoid technology in biomedical research. The authors hypothesized that disease models could be the main focus of organoid research in the future and that organoids could also be used to test the efficacy and toxicity of drug compounds and even in whole-organ replacement in the clinic. Clevers (27) published the fourth-most cited review (n=867) in *Cell* in 2016, wherein he described the state of the exponentially developing field of induced pluripotent stem cell (iPSC)- and ASC-based organoids. Clevers also pointed out that current modes of preparation of organoids had some limitations, such as their lack of blood vessels and immune cells, which results in only the partial recapitulation of disease processes. The fifth-most cited article (n=865) was published by Qian *et al.* (28). They invented a miniaturized spinning bioreactor to culture brain-region-specific organoids based on human iPSCs. These authors then used organoids to model the exposure of the forebrain to the ZIKV, demonstrating that both African and Asian ZIKV strains preferentially and productively infect neural progenitors in organoids. Their organoids and bioreactor provided an accessible and versatile platform for compound testing of the ZIKV. Next, van de Wetering *et al.* (29) published the sixth-most cited study in *Cell* in 2015, with 805 co-citations; it reported the construction of tumor organoid cultures from 20 consecutive colorectal carcinoma (CRC) patients. The authors showed that these tumor organoids closely recapitulated several properties of CRC, such as somatic copy number and mutation spectra, and the organoids were amenable to high-throughput drug screening, enabling the design of personalized therapy. In 2015, Boj *et al.* (30) published the seventh-most cited article, also in *Cell* (n=793). They reported the establishment of pancreatic organoids as a tractable and transplantable system with which to investigate the molecular and cellular characteristics of mouse and human tumor progression. In particular, the authors successfully generated a normal ductal architecture after orthotopic transplantation. They also found that

nucleoporins are broadly upregulated in neoplastic murine organoids, which indicates that they could be associated with the initiation of cancer development. The eighth-most cited article was published in *Cell Stem Cell* by Spence *et al.* (34). This article illustrated that a series of growth factors, such as WNT3A and FGF4, can be manipulated to direct the differentiation of human iPSCs into intestinal tissue and mimic embryonic intestinal development *in vitro*. The ninth-most cited article (n=663) was published in *PNAS* in 2005 by Gao *et al.* (11), who reported the successful construction of a long-term culture of prostate cancer organoids from biopsy specimens and circulating tumor cells. They also generated models of key prostate-specific genetic alterations, including *ETS*-translocations, *SPOP* mutations, *FOXA1* mutations, and *CHD1* loss. The tenth-most cited article (n=604) was published in *Nature Cell Biology* and was written by Garcez *et al.* (32). In this article, the authors examined the influence of ZIKV infection on human neural stem cells forming brain organoids, which suggests that ZIKV damages neurogenesis during human brain development.

Knowledge base

The number of co-cited articles represents how frequently at least two publications are cited together by other publications and thus can be considered a knowledge base for a specific field or subject (36). Our study selected the top 10 co-cited references to define the knowledge base related to organoid research. Among them, eight articles were also found on the list of the top 10 cited references as well as the list of the top 10 co-cited references, which indicated that these publications were not only part of the knowledge base but were also considered influential studies. The other two publications were "Single Lgr5 stem cells build crypt-villus structures *in vitro* without a mesenchymal niche" and "Vascularized and functional human liver from an iPSC-derived organ bud transplant". The former is the most co-cited article (n=574) and was published by Sato *et al.* (33). In it, the authors illustrated that a single Lgr5+ intestinal stem cell could operate independently of positional cues from its environment and generate a sustained, expanding, self-organizing epithelial structure similar to a normal gut. The latter paper is the tenth-most co-cited article, published by Takebe *et al.* (35), who used human iPSCs to generate liver buds *in vitro* (iPSC-LBs), which can eventually differentiate into a vascularized and functional human liver after transplantation.

Hot topics, limitations of existing studies, and possible future solutions

According to our analysis, the main current hot topics in organoid research concern drug screening (29,37-39), disease modeling (used to identify human-specific disease mechanisms) (24,26,40-42), personalized medicine/precision medicine (43,44), tissue engineering (regenerative medicine) (45-47), developmental biology (48-51). These topics are likely to be the key research directions in the future. However, there are still some limitations in the current organoid research, which concern the lack of reproducibility, the limited level of maturity and function, and the absence of appropriate functional readouts. The lack of reproducibility is the most severe problem. This is because the formation of organoids mainly depends on a self-organization principle with minimal control over the external inputs supplied to the system. In addition, the uncontrolled nature of these processes leads to high heterogeneity in the current organoid systems among different laboratories (52). Thus, achieving robust and reproducible organoid cultures is a priority, as only then will it be possible to utilize them in basic and clinical studies. Applying bioengineering strategies to control organoids' micro-environments by integrating chemical (such as the chemical modification of hydrogels) and physical instructions (such as geometry and mechanical properties) could be essential to control organoid self-organization and differentiation. Thus, instead of culturing organoids without any constraints, researchers should adopt some biomimetic hydrogels (53) and well-defined engineering technologies, such as micropatterning techniques (54), extracellular matrix (ECM) dynamics (55), and microfluidic technology (56), to ensure the homogeneity of organoids in a highly controlled manner-both spatiotemporally and in terms of dosage. Further studies are required to realize the potential of these bioengineering strategies in the organoid field. Furthermore, standardized protocols with a tendency toward more complex systems should be developed to achieve superior homologous organoids.

Another significant limitation is the reduced level of maturity and function. None of the current organoid systems can mimic the full functional repertoire of the organs. The main reasons are the limited lifespan of organoids, the loss of a mesenchymal compartment, vascularization, and/or microbiome. For example, the limited lifespan leads to dead cells accumulating in the hollow lumen in cystic epithelial organoids (24). Brain organoids

generally fail to mature beyond a fetal phenotype (57). The potential solution to this shortcoming could be the promotion of vascularization, tissue-tissue interactions, and mimicking physiological environments. Vascularization in organoids enables the convective transport of nutrients/gases and waste removal, increasing the organoid lifespan and the size and complexity compared to static culture systems (58), while it is also difficult to achieve stable and mature microvascular networks within organoids. Engineering tissue-tissue interactions could be another solution to increase the level of organoid maturity since the morphology of organs is mediated by signals from adjacent tissues. Some examples are the generation of intestinal tissues with a functional enteric nervous system (59) and the recapitulation of human hepato-biliary-pancreatic tissue-tissue boundaries (60), although these approaches need optimization to achieve organoid to organoid integration with the ability to recapitulate the development *in vivo*. Some micro-technology, such as the organ-on-a-chip, can mimic physiological-like environments and theoretically capture key aspects of (human) organ physiology. In the future, coupling organ-on-a-chip systems may increase our understanding of complex inter-organ behaviors in health versus disease scenarios.

The absence of appropriate functional readouts is also a crucial limitation. Currently, organoid research mainly depends on phenotypic readouts, including aspect, shape, and number of organoids, which provide only limited information about the functionality of the organoids. Thus, continuous, accurate, and versatile functional readouts, such as image-based analyses (61), *in situ* electrochemical probing (62), and high-throughput setups (63), will enable the detection of subtle cellular responses and achieve a precise characterization of organoids in the future. These solutions are likely to become hot topics in the future, as they promote the further application of organoids for drug screening, disease modeling, and personalized medicine/precision medicine.

Strengths and limitations

To the best of our knowledge, this is the first investigation to employ measurement analysis of organoid research trends. Publications in this field were collected and fully investigated by quantitative and qualitative analysis, as was research quality across different authors, using the R bibliometrix package. Two well-known scientometric software tools (VOSviewer and CiteSpace) were used to construct and visualize the bibliometric networks through co-authorship, co-citation, and co-occurrence analyses, and the top 90 articles with the strongest citation bursts were identified. However, our study has some limitations. First, our searches were only conducted in the WoS database, and the accuracy of our analyses could be improved by accessing other databases as well. Second, the results obtained from the bibliometric analysis may not be comprehensive; it is possible that some information considered important in this field may have been published in articles other than those in our analyses. Finally, it is possible that we have not paid sufficient attention to some important recent publications and have not discussed them in sufficient detail.

Conclusions

Our results indicate that the United States has made the largest contribution to organoid research, while Hans Clevers of the University Medical Center Utrecht in the Netherlands has made the most significant individual impact. Most related studies have been published in high-quality journals, revealing that progress in this field is considered very meaningful. Recent articles with strong citation bursts are good indicators of future research topics. Using various analyses, we found changing trends from "methods to build organoids (e.g., "lgr5$^+$ stem cell" and "3D culture") to "practical applications of organoids" (e.g., "cystic fibrosis" and "Zika virus"). The main hot topics currently are drug screening, disease modeling, personalized medicine/precision medicine, tissue engineering (regenerative medicine), and developmental biology, and they may still be hotspots in the future. However, there are still some limitations, such as the lack of reproducibility, the low level of maturity and function, and the absence of appropriate functional readouts. Possible solutions involve the development of bioengineering strategies to ensure the homogeneity of organoids, the promotion of vascularization, tissue-tissue interactions, and mimicking physiological environments to increase the organoid maturity and function, as well as the development of accurate and versatile functional readouts to provide more information about the functionality of the organoids.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-290/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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