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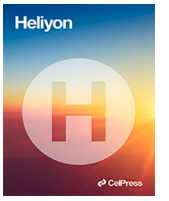

Research article

Deciphering two decades of cellular reprogramming in cancer: A bibliometric analysis of evolving trends and research frontiers

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ABSTRACT

Recent research has reevaluated the traditional view of cancer's linear progression and recurrence by introducing cellular reprogramming a process in which cancer cells can their state under certain conditions. This change is driven by a combination of genetic and epigenetic factors, with pivotal roles played by key genes, and pathways, notably Wnt and Notch. The complexity of cancer's behavior is further influenced by factors such as the epithelial-mesenchymal transition (EMT) and therapy-induced stress, both of which are significant contributors to cancer recurrence. In this context bibliometric analysis emerges as a crucial tool for evaluating the impacts and trends within scientific literature. Our study utilized bibliometrics to analysis the role of cellular reprogramming oncology over the past two decades, highlighting its potential to improve cancer treatment outcomes. In conducting this analysis, we searched for literature search on cellular reprogramming (CR) in the Web of Science database, covering the years 2002–2022. We employed visualization tools like Citespace, VOSviewer, and Bibliometrix to analyze the collected data resulting in a dataset of 3102 articles. The United States and China emerged as leading contributors to this field, with the University of Texas MD Anderson Cancer Center being the most prolific institution. Menendez was the most influential scholar in this research domain. Cancers was the journal with the most publications on this subject. The most local-cited document was the article titled "Hallmarks of Cancer: The Next Generation". A comprehensive analysis has been conducted based on keywords and cited references. In recent years, the research emphasis has shifted to "extracellular vesicles," "cancer therapy," and "cellular plasticity". Therefore, this analysis uses bibliometrics to chart cutting-edge progress in cancer's cellular reprogramming, aiding experts to quickly understand and innovate in this crucial area.

1. Introduction

The journey of cancer from its beginning to its comeback has often been seen as a step-by-step process. But new studies are changing

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this view by showing how cancer cells can change their behavior under certain conditions through cellular reprogramming [1]. This exciting area of research is especially important in cancers with unusual growth patterns [2,3]. The possibility that reprogramming could turn cancerous cells back to a non-cancerous state is sparking a lot of interest [4,5]. It shows how the environment around cells, along with their genetic makeup and changes in gene expression [6], play a role. Key players in this new view include the Wnt and Notch [7] signaling pathways, as well as processes like EMT [8] and cell fusion. Key players in this new view include the Wnt and Notch signaling pathways, as well as processes like EMT and cell fusion [4,9]. Understanding all these factors is crucial for developing better treatments and improving patient outcomes [1]. Cellular reprogramming holds a potentially key role in understanding and treating cancer, especially through the application of biomaterials [11], the study of tumor organoids [12], and the exploration of the immune microenvironment [13]. Within this context, bibliometrics emerges as a critical tool, employing quantitative analyses to dissect the proliferation of medical literature [10]. It involves aggregating, structuring, and scrutinizing bibliographic data, embracing aspects such as citation metrics, co-authorship patterns, and publication outlets. Bibliometrics offers numerous advantages, including its ability to delineate and quantify research consequences, provide data-driven assessments of scholarly productivity, and track the spread and impact of studies over time [13]. Furthermore, bibliometrics can bolster the discernment of research trajectories, nascent domains, and scholarly synergies, thereby highlighting strategic envisioning and resource orchestration within research establishments. Amid the ongoing growth of scholarly materials and the increasing importance of the impact of research, bibliometrics remains vital for assessing and measuring scholarly endeavors.

This bibliometric study aimed to provide an extensive overview of the present understanding of cellular reprogramming within the domain of medical oncology. The central research question addressed in this study pertains to the contemporary state of knowledge and clinical experience regarding the use of cellular reprogramming as a therapeutic approach in cancer studies. The results of this investigation revealed the promising potential of cellular reprogramming in both preclinical and clinical trials. Several studies have reported superior treatment outcomes, compared with those of conventional modalities. Nonetheless, existing literature underscores the need for further in-depth research. These efforts are necessary to elucidate the intricate mechanisms underlying the efficacy of cellular reprogramming and optimize treatment protocols.

The primary objective of this study was to bridge the existing knowledge gaps by amalgamating recent discoveries and emerging trends in cellular reprogramming. This comprehensive article provides an invaluable resource for diverse audiences, including medical researchers, clinicians, and healthcare policy decision-makers.

2. Material and methods

2.1. Search strategy

We conducted a literature search on the Web of Science Core Collection (WoSCC) [14] database (https://www.webofscience.com/wos/woscc/basic-search) on February 16, 2024. The search formula is ((TS=(cellular reprogramming)) AND TS=(“cancer”OR“tumor”OR“neoplas”OR“malignan”OR“carcinoma”OR“adenocarcinoma”OR“choricarcinoma”OR“leukemia”OR“sarcoma”OR“melanoma”)) AND LA = (English). The time frame of the publication is limited from 2002 to 2022.

To ensure accuracy and objectivity in our analysis, only English-written articles and review articles were considered, excluding other document types such as meeting abstracts, proceeding papers, and editorials. After the initial search, the retrieved records were thoroughly evaluated for relevance through a review of their titles, abstracts, and full texts by two independent researchers. This process led to the refinement of the dataset, with non-relevant entries being systematically removed. The final collection of documents was downloaded in both “BibTeX” and “Plain text file” formats, featuring “Full Record and Cited References,” to facilitate an in-depth analysis of the data. This methodical approach ensured the collection of a precise and unbiased dataset, with all data retrieval and selection processes completed within a single day to avoid any inconsistencies due to potential database updates.

2.2. Data analysis

VOSviewer (version 1.6.18) is a sophisticated bibliometric analysis tool, adept at distilling essential insights from a vast array of publications [15]. Commonly utilized for constructing collaboration, co-citation, and co-occurrence networks, this software has been cited in numerous studies. In the context of our research, VOSviewer facilitated an array of analyses, encompassing country and institution metrics, journal and co-cited journal evaluations, author and co-cited author examinations, and keyword co-occurrence investigations. Within the VOSviewer-generated maps, nodes signify entities like countries, institutions, journals, and authors. The magnitude and hue of a node delineate the quantity and categorization of these entities, respectively, while the thickness of connecting lines mirrors the intensity of collaboration or co-citation between nodes. In this project, VOSviewer was utilized to 1) map institutional collaboration networks, uncovering connections between organizations, 2) analyze national cooperation networks, showcasing global research partnerships, and 3) explore keywords co-occurrence networks, highlighting key research themes and trends.

On the other hand, CiteSpace (version 6.1. R1), crafted by Professor Chen C, serves as another potent instrument for bibliometric analysis and visualization [16]. In our effort, CiteSpace was instrumental in generating dual-map overlays of journals and conducting an in-depth analysis of references with Citation Bursts, further enriched by an examination of keyword Bursts over the past five years and a focused analysis of the most recent year’s Bursts to capture the evolving dynamics and emerging trends in the field.

Further deepening our analysis, we leveraged the R package “bibliometrix” (version 3.2.1) (https://www.bibliometrix.org) to conduct a thematic evolution scrutiny and to architect a comprehensive distribution network encompassing cellular reprogramming publications within the realm of cancer [17]. Metrics like the quartile and impact factor of journals were sourced from the Journal

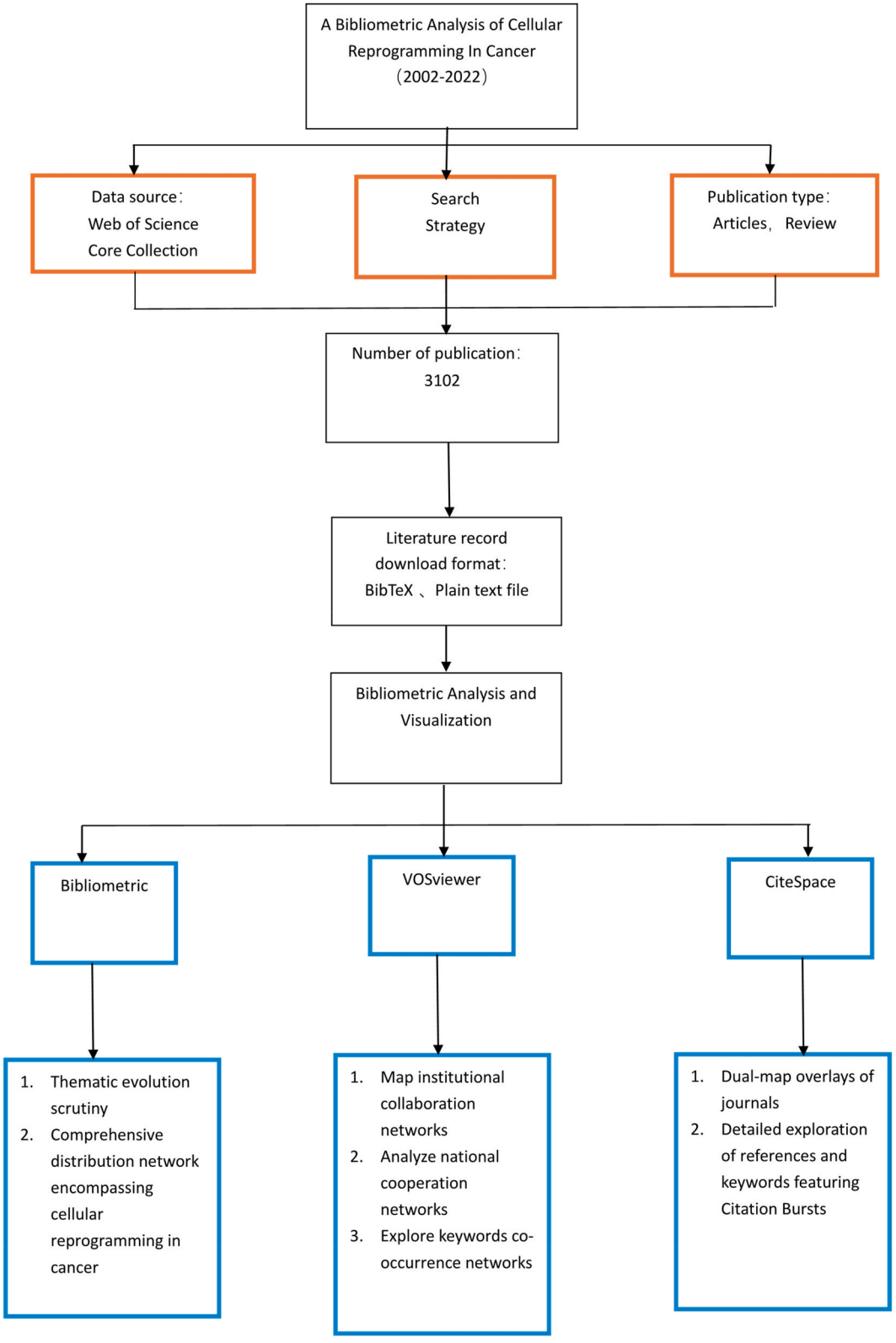

Fig. 1. Flow-chart of the study.

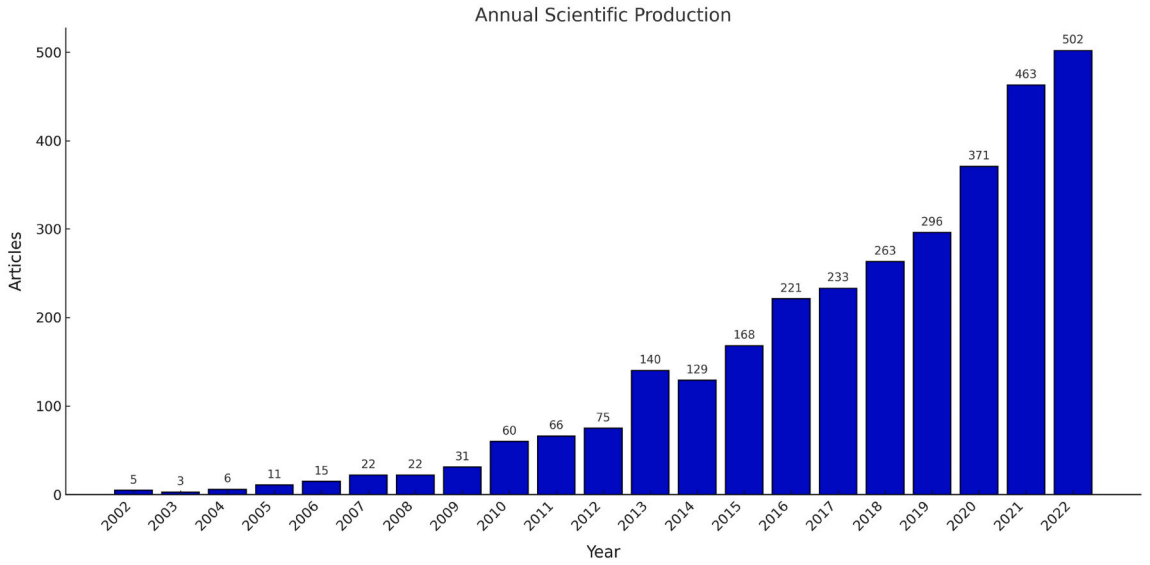

Fig. 2. Number of publications per year and the cumulative number.

Citation Reports 2020. Moreover, for a granular quantitative assessment of publications, we employed Microsoft Office Excel 2019.

3. Results

3.1. Publications and citations

According to our research schematic, a cumulative total of 3102 scientific papers pertaining to cellular reprogramming in oncology have been published over the last two decades (Fig. 1). This includes 1954 "articles" and 1148 "reviews." The entire temporal span can be divided into two discrete epochs: Phase I (2002–2012) and Phase II (2013–2022). As delineated in our discoveries, the average annual number of publications in Phase I was approximately 28.73, suggesting that the domain of cellular reprogramming in oncology is still in its infancy. However, in Phase II, the volume of publications significantly increased, averaging an impressive 278.6 articles annually. Specifically, the number of pertinent publications in 2013 was 1.87-fold higher than that in 2012. In 2022, the annual number of publications on cellular reprogramming in oncology was 502. Over the last decade (Phase II), the bulk of publications have witnessed a brisk and substantial upswing when juxtaposed with Phase I, signifying burgeoning intrigue and progression in this realm of inquiry (Fig. 2).

3.2. Analysis of countries

Literature on cellular reprogramming in the context of cancer includes contributions from 53 countries. As depicted in Fig. 3A, the United States led the pack with 1277 publications, accounting for 29.4% of the total publications. China followed closely with 580 publications, accounting for 13.3%, followed by Germany with 249 publications, contributing 5.7%. From 2002 to 2022, these three nations collectively represent 49.9% of all publications in this domain. Fig. 3B illustrates the leading countries in terms of total citations, with the United States, Switzerland, and China occupying the top three positions. The United States accumulated 144,160 citations, Switzerland 47,816, and China 21,096. In the realm of global collaborative networks, numerous collaborative endeavors have been identified, with the most prominent being the USA-China (128 collaborations), USA-Germany (62 collaborations), and USA-UK (44 collaborations) networks, as depicted in Fig. 3C.

3.3. Analysis of institutions

During the temporal span from 2002 to 2022, an aggregate of 395 entities tendered manuscripts on the topic of cellular reprogramming in oncology. As shown in Table 1, the three apex institutions at the forefront in this realm are the University of Texas MD Anderson Cancer Center with 70 delineations, Harvard Medical School with 65 delineations, and Harvard University with 61 delineations. Collaborative network scrutiny included institutions with 15 or more delineations, which were subsequently displayed using VOSviewer. The clusters were hue-differentiated, as predicted by the magnitude of collaboration among the organizations (Fig. 4A). The most vigorous cooperative nexus was discerned between the Chinese Academy of Sciences and University of the Chinese Academy of Sciences, with a link robustness of 18. This indicates that they are interconnected by the most common line, signifying a profound degree of collaboration.

In the chronological delineation of the institution co-authorship nexus illustrated in Fig. 4B, the median publication number of an

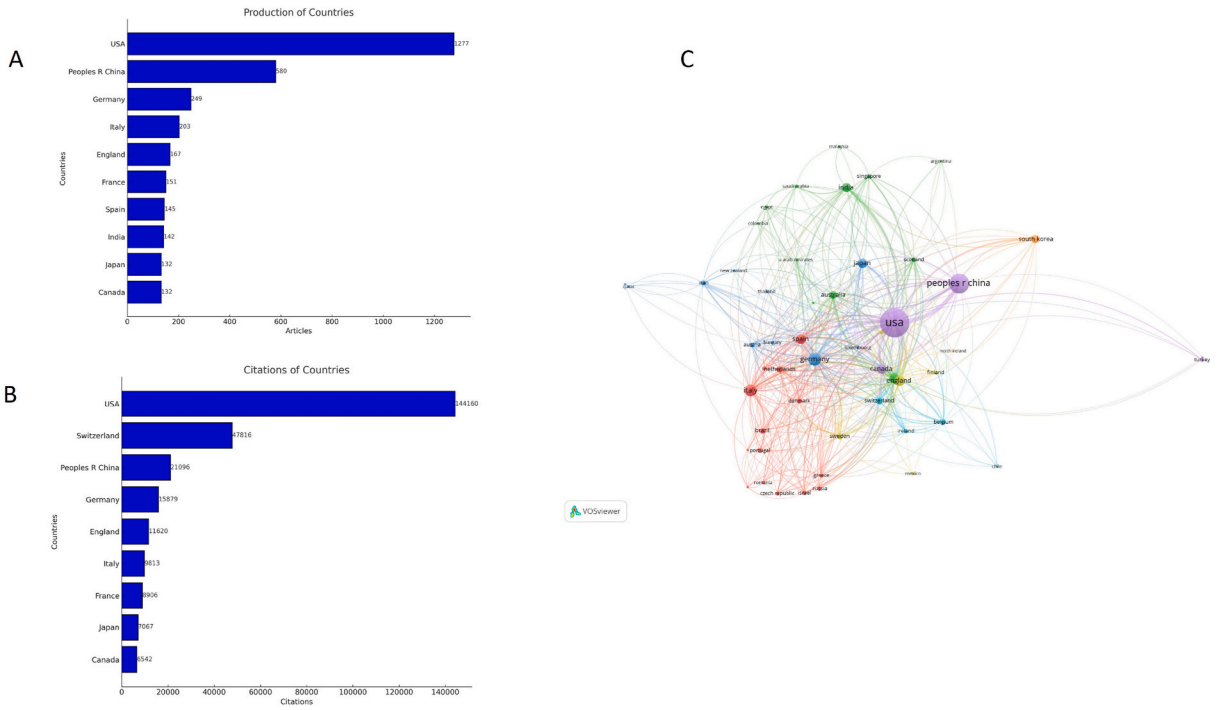

Fig. 3. A) Each country's contribution to the cellular reprogramming in cancer. B) Analysis of total citation counts by country in the field of cellular reprogramming in cancer. C) Principal bilateral collaborations in the global cooperation network of cellular reprogramming in cancer.

Table 1
Top 10 institutions in the field of cellular reprogramming in cancer.

RANK	Institution	Country	Publication	Total citations	Average citations
1	University of Texas MD Anderson Cancer Center	USA	70	10420	148.86
2	Harvard Medical School	USA	65	3426	52.71
3	Harvard University	USA	61	12386	203.05
4	University of Pennsylvania	USA	60	12402	206.7
5	National Cancer Institute	USA	56	3492	62.36
6	Chinese Academy of Sciences	China	49	2808	57.31
7	Shanghai Jiaotong University	China	45	2363	25.51
8	Sun Yat-Sen University	China	44	1759	39.98
9	Stanford University	USA	40	2900	72.5
10	Fudan University	China	37	1310	35.4

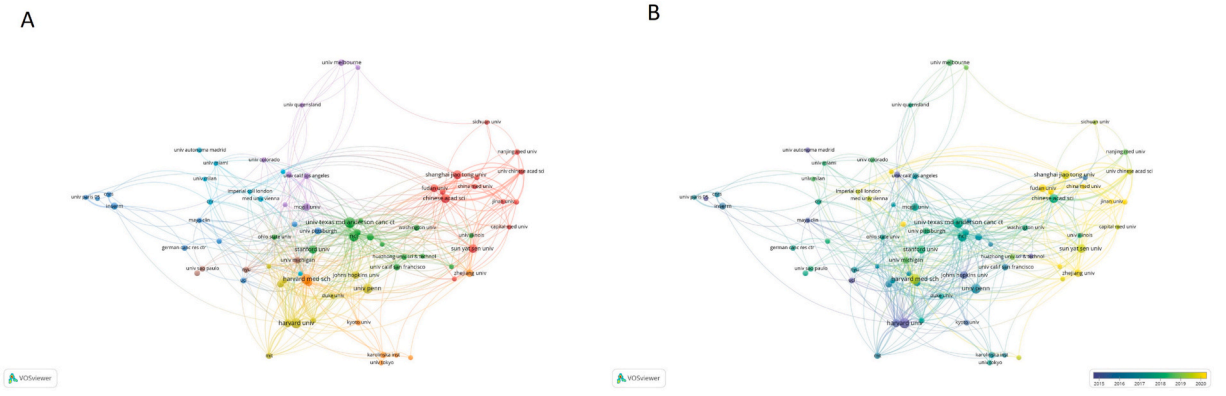

Fig. 4. A) Cooperation network for institutions B) Dynamics and trends of institutions over time. In the network visualization, nodes represent institutions, and their size reflects the number of publications. Lines between nodes indicate cooperation relationship.

Table 2
Top 10 authors in the field of cellular reprogramming in cancer.

Rank	Author	Institution	Publication	Total citations	h-index	g-index
1	Menendez JA	Institut Català d'Oncologia	16	701	13	17
2	Cuezva JM	Universidad Autónoma de Madrid	12	636	10	13
3	Cuyàs E	Institut Català d'Oncologia	10	461	8	9
4	Mischel PS	Ludwig Institute for Cancer Research	10	551	8	8
5	Cavenee WK	University of California, San Diego	9	539	9	9
6	Masui K	Tokyo Women's Medical University	9	539	9	9
7	Thompson CB	Memorial Sloan Kettering Cancer Center	9	11172	7	7
8	Corominas-Faja B	Institut Català d'Oncologia	8	477	3	3
9	DeBerardinis RJ	University of Texas Southwestern Medical Center at Dallas	8	5043	7	7
10	Vazquez-Martin A	Institut Català d'Oncologia	8	537	8	8

institution is symbolized by the node's hue, adhering to a chronological gradient. Harvard University, with a median per annum publication of 2013.74, was depicted in a profound azure tint, insinuating that scholars from this academia were predominantly operative during that particular epoch in the research domain. Conversely, Central South University, with a median publication annum of 2020.68, was exhibited in a luminous amber shade, signifying that this institution's scholarly endeavors in the field were of a more recent vintage.

3.4. Analysis of authors

The literature on cellular reprogramming in cancer was contributed by 18,338 authors; the 10 most noteworthy contributors are outlined in Table 2. Menendez, from the Institut Català d'Oncologia, emerged as the most impactful author, having penned 16 papers, and amassed 701 citations. Following closely were Cuezva, JM from Universidad Autónoma de Madrid, Cuyàs, E from the Institut Català d'Oncologia and Mischel, PS from Ludwig Institute for Cancer Research. However, the publication output of the other authors on this list fell below 10. In terms of the h-index and g-index metrics, Menendez, Cuezva, Cavenee, and Masui led the ranks, showcasing their extensive influence in the field. Fig. 5 presents a timeline visualization that emphasizes the activities of the top 10 researchers and their publication trends throughout the years.

3.5. Analysis of journals

In the field of cellular reprogramming in cancer, 3102 papers have been published in 845 journals. Table 3 shows the top 10 journals that have made significant contributions to this field. "Cancers" stands out as the foremost journal, with 120 publications, constituting 3.9% of all papers in this domain. This was closely followed by International Journal of Molecular Sciences (83, 2.7%), Frontiers in Oncology (72 articles,2.3%), Scientific Reports (50 publications (1.6%), and Nature Communications (49 articles, 1.6%). Collectively, these journals represent 26.1% of the total publications on cellular reprogramming in cancer.

The impact factor (IF) is an estimated metric that assesses the prestige of a journal in specific areas based on its co-citation frequency. A higher IF indicates that the articles published in a journal receive more citations, rendering the journal more influential in its field. Journals with higher IFs were perceived as more authoritative in their respective domains. As illustrated in Table 3, Nature

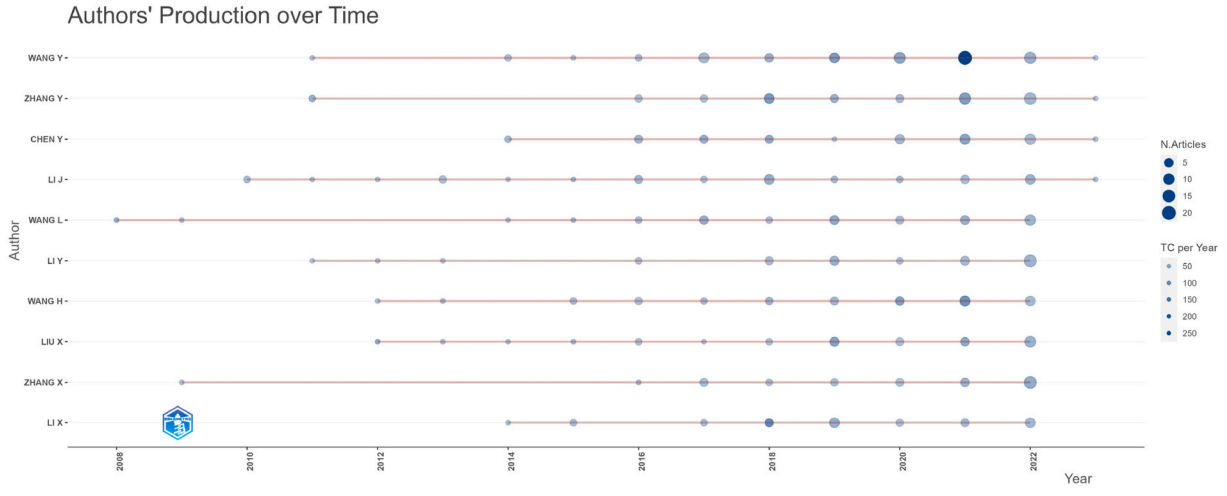

Fig. 5. Timeline visualization for the top ten active researchers. The number of publications and citations are represented by the size and color of the node, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Top 10 Journals in the field of cellular reprogramming in cancer.

Rank	Journal	Publication	Country	If (2022)	JCR region	Co-cited Journal	citations	If (2022)	JCR region	Country
1	Cancers	120	Switzerland	5.2	Q2	Nature	11648	64.8	Q1	UK
2	International Journal of Molecular Sciences	83	Switzerland	5.6	Q2	Cell	9775	64.5	Q1	US
3	Frontiers in Oncology	72	Switzerland	4.7	Q2	Proceedings of the National Academy of Sciences of the United States of America	8038	11.1	Q1	US
4	Scientific Reports	50	UK	4.6	Q1	Cancer research	8019	11.2	US	Q1
5	Nature Communications	49	UK	16.6	Q1	Journal of Biological Chemistry	6772	4.8	US	Q2
6	Proceedings of the National Academy of Sciences of the United States of America	47	US	11.1	Q1	Science	6282	56.9	US	Q1
7	Frontiers in Immunology	46	Switzerland	7.3	Q1	Oncogene	4626	8	UK	Q1
8	Oncogene	44	UK	8	Q1	PLOS ONE	4214	3.7	US	Q2
9	PLOS ONE	44	US	3.7	Q2	cancer cell	4072	50.3	US	Q1
10	Frontiers in Cell and Developmental Biology	43	Switzerland	5.5	Q2	Nature Reviews Cancer	3653	78.5	UK	Q1

emerged as the most frequently cited journal, with a citation count surpassing 11,637. The second place, in terms of citation frequency, was secured by “Cell,” with 10,291 citations. Following closely are the “Proceedings of the National Academy of Sciences of the United States of America” (8666), “Cancer Research” (8217) and " J Biol Chem” (7270), The citation interconnections between journals and co-cited journals are clarified through a dual-map overlay of journals that displays conglomerates of citing journals on the port side and conglomerates of cited journals on the starboard side. As illustrated in Fig. 6, the tangerine trajectory serves as the primary conduit for citations, indicating that most citations are directed towards research articles published in molecular, biological, or genetic journals.

3.6. Analysis of references

Of the 3102 manuscripts that scrutinized cellular reprogramming in oncology, the 10 most-cited papers accounted for37.7% of the total citations. Table 4 presents a list of the 10 most-cited sources, arranged in descending order based on their co-citation frequency. Each article has been cited on more than 25 occasions. Most of these articles originated in the United States, with a few exceptions from prominent research institute worldwide. The most-cited article, titled “Hallmarks of Cancer: The Next Generation,” was promulgated in the revered journal “Cell,” which emerged as the most recurrently cited journal in this specialized domain.

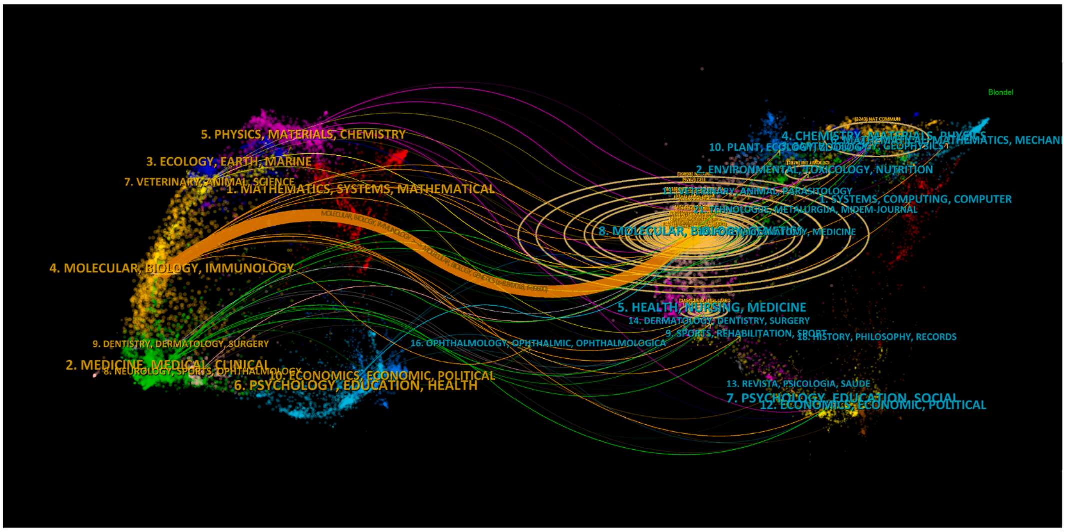

Fig. 6. Double image overlay of journals. Image parameters: a: 1; source circle size: 40; target circle size: 5; captured center point (radius): 0. The citing journals are located on the left, and the cited journals are located on the right. The colored paths (one orange and two green reference paths) represent the citation relationships. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Analysis of citation impact of top 10 highly cited articles on cellular reprogramming in cancer.

Rank	Document	DOI	Local citations	Global citations
1	HANAHAN D, 2011, CELL	10.1016/j.cell.2011.02.013	557	44499
2	PAVLOVA NN, 2016, CELL METAB	10.1016/j.cmet.2015.12.006	197	3381
3	WARD PS, 2012, CANCER CELL	10.1016/j.ccr.2012.02.014	167	2279
4	DEBERARDINIS RJ, 2008, CELL METAB	10.1016/j.cmet.2007.10.002	140	2961
5	UTIKAL J, 2009, NATURE	10.1038/nature08285	66	661
6	SON J, 2013, NATURE	10.1038/nature12040	61	1386
7	MOSTEIRO L, 2016, SCIENCE	10.1126/science.aaf4445	48	392
8	KALLURI R, 2016, NAT REV CANCER	10.1038/nrc.2016.73	29	2474
9	MILANOVIC M, 2018, NATURE	10.1038/nature25167	28	606
10	SEMENZA GL, 2013, J CLIN INVEST	10.1172/JCI67230	27	933

CiteSpace software was employed to perform burst and cluster analyses of cited references within the domain of cellular reprogramming in the context of cancer. In bibliometric investigations, bursts in references can denote trending topics or research hotspots. Fig. 7A shows the top 15 cited references that experienced significant citation spikes between 2002 and 2022. The magnitude of these bursts exhibited variabilities ranging from 13.45 to 60.40. The cerulean line segment serves as a demarcation for temporal duration, whereas the scarlet line segment represents periods of heightened citation activity.

The trio spearheading the list in terms of robust citation bursts are as follows: “Hallmarks of Cancer: The Next Generation [18]" (strength: 60.40; publication year: 2011)This review presents a nuanced exploration of an emerging hallmark of cancer: the intricate reprogramming of energy metabolism. “The Emerging Hallmarks of Cancer Metabolism” [19] (strength: 40.30; publication year: 2016) This review highlights that oncogenic mutations reprogram cancer cell metabolism, affecting nutrient uptake and microenvironment interactions, which could guide tumor classification and treatment. The article titled “Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation” [20] (strength: 31.36; publication year: 2009). This review highlights that cancer cells reprogram their metabolism to prioritize biomass production over efficient energy generation, a shift central to their proliferation and a potential therapeutic target. These references, notable for their significant impact, have shaped the discourse and expanded the knowledge of cellular reprogramming in the context of cancer.

The topic clustering map of the cellular reprogramming in cancer study field, as depicted in Fig. 7B, reveals the presence of 10 noteworthy clusters. These clusters were characterized by their modularity and silhouette scores: $Q = 0.7794$ and $S = 0.9178$, respectively. The aforementioned variables play a crucial role in evaluating the coherence and dependability of grouping in the visualization. Q-values greater than 0.3 and the S values higher than 0.5 indicate the presence of a strong and reliable clustering structure.

The cluster that exhibited the greatest significance was designated as “reprogramming” [21] thus, establishing the foundation for the research theme. Following closely were the clusters emphasizing the “metabolic modeling” [22] (cluster #1), “induced pluripotent stem cells” [23] (cluster #2), and “pancreatic cancer” [24] (cluster #3). Delving deeper into the research landscape, other notable clusters that emerged included H + -ATP synthase, induced cancer stem cells, metabolic reprogramming, metabolic immunotherapy, and differentiation. Collectively, these clusters provide a comprehensive overview of the multifaceted domains of cellular reprogramming in cancer.

3.7. Analysis of keywords

Keyword analysis was conducted using VOSviewer and CiteSpace software programs. Considering the clarity of visualization, the threshold for keyword occurrence was set at 10, and 800 keywords qualified for analysis.

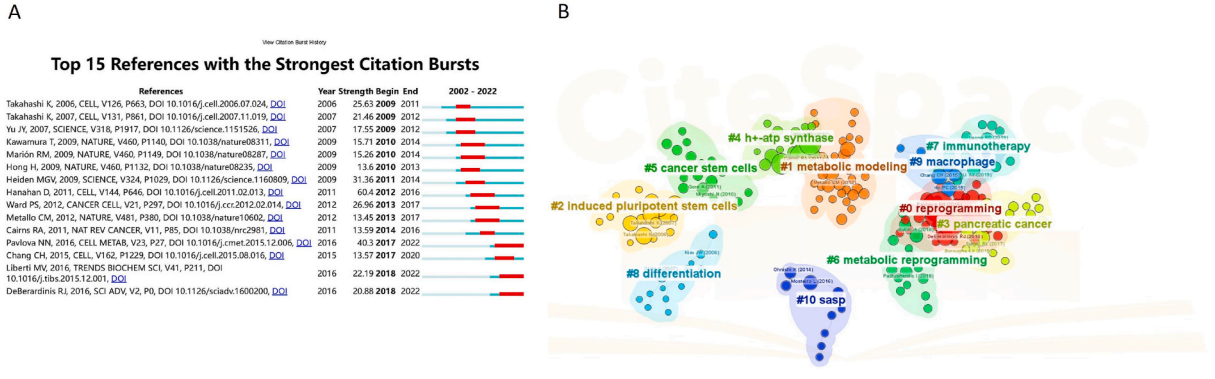

Fig. 7. A) List of the 15 references with the strongest citation bursts. B) Cluster visualization for cited references.

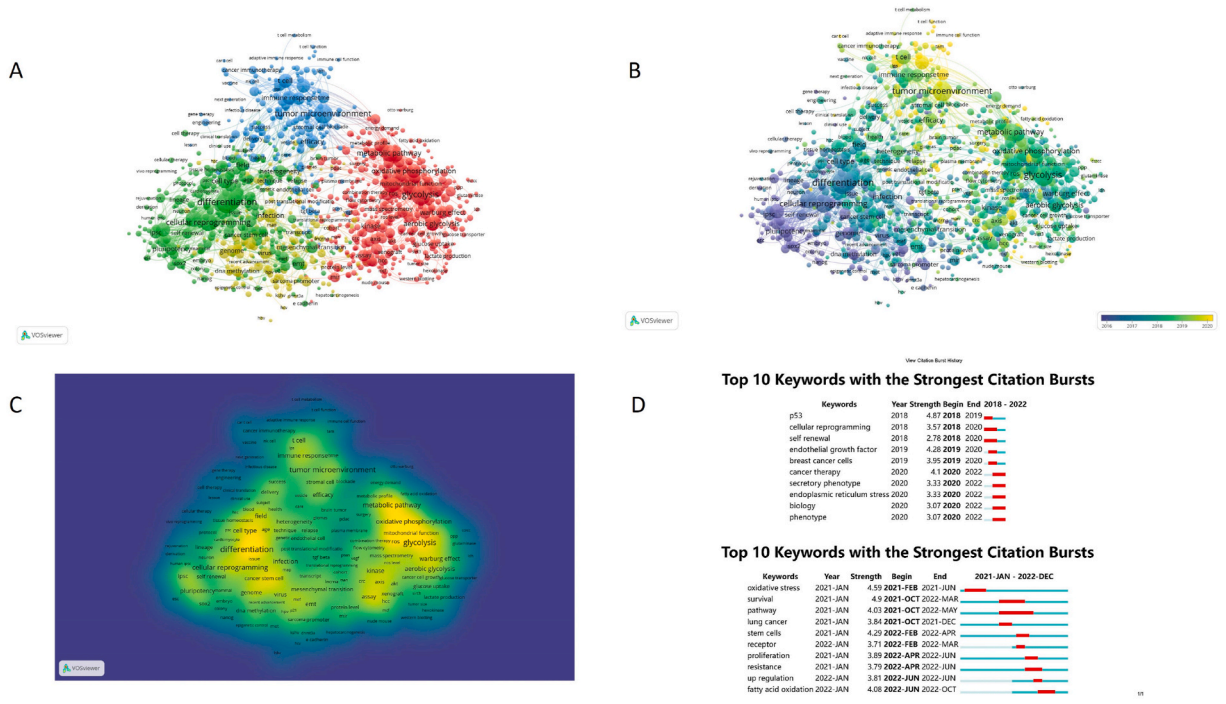

Fig. 8. A) Cluster visualization for keywords. B) Timeline visualization for keywords. C) Frequency visualization for keywords. D) The 10 keywords with the strongest citation bursts.

As shown in Fig. 8A, the keywords are systematically arranged into four clusters, each distinguished by unique colors. In cluster 1, "glycolysis" emerged as the predominant node. Accompanying this central theme were other significant nodes such as oxidative phosphorylation, aerobic glycolysis, metabolic pathway, kinase, warburg effect, and mitochondrium. This cluster primarily delved into the intricate relationship between glucose metabolism and cellular reprogramming in cancer. Cluster 2 was anchored using the keyword "differentiation." Other central nodes in this cluster included cellular reprogramming, cell type, pluripotency, cancer stem cell, heterogeneity, and differentiated cell. Here, we focused on the dynamic processes of cell differentiation and how cellular reprogramming influences the behavior of cancerous cells. In cluster 3, "tumor microenvironment" stood out as the central node. Augmenting this theme included nodes such as efficacy, immune response, T cells and cancer immunotherapy. This cluster encapsulates the intricate interactions between the tumor microenvironment and how it affects cellular reprogramming in cancer, emphasizing the immune system's role. Finally, cluster 4 was centered around the keyword "genome." This cluster predominantly investigates genomic transitions, particularly DNA methylation, and its implications in cellular reprogramming in cancer. Together, these clusters provide a comprehensive landscape of current research directions and thematic concentrations in the domain of cellular reprogramming in cancer.

A timeline visualization of keywords related to cellular reprogramming in the field of cancer is shown in Fig. 8B. The hue of each node represents the median occurrence epoch, following a chronological gradient. The keyword "dna methylation" (with a median occurrence epoch of 2015.61) is shown in blue, indicating its prominence as a focal point in the antecedent stages of research in this sphere. In contradistinction, the keyword "TME" (an abbreviation for tumor microenvironment, with a median occurrence epoch of 2020.79) was presented in yellow, suggesting its burgeoning significance and more recent activity within the realm of cellular reprogramming in oncology. This visual rendering provides insight into the evolving focal areas within the research terrain over time.

A heatmap, as seen in Fig. 8C, was used to illustrate the frequency of occurrence of the terms, with the yellow zone indicating a high frequency. The keyword that appeared most frequently in the text was "glycolysis." Other notable terms that were frequently mentioned were "differentiation," "cellular reprogramming," "tumor microenvironment," and "oxidative phosphorylation."

A comprehensive visual representation of citation bursts for the most frequently used keywords is presented in Fig. 8D. Burst duration and time interval are indicated in red and blue, respectively. This representation offers chronological insights into evolving research hotspots in the domain of cellular reprogramming in cancer. For the past 5 years (2018–2022), the discernible citation bursts for the top 10 keywords indicate a shift in research focus. Keywords such as "p35," "endothelial growth factor," and " cancer therapy," dominated the academic dialogue, reflecting the broader themes and prevailing interests of this period. In recent years (2021–2022), citation bursts for the top ten keywords hinted at an evolving landscape with emerging research areas. "oxidative stress" and "survival" have taken center stage. This indicates a more specialized focus on distinct cancer forms such as pancreatic cancer, intricate cellular processes including oxidative stress and receptor survival, and specific metabolic pathways like glutamine metabolism in stem cells, all within the realm of cellular reprogramming.

4. Discussion

4.1. The global research dynamics in the field of cellular reprogramming in cancer

In this age of rapid information expansion, maintaining a clear understanding of the latest advancements in any field is a significant feat. To shed light on global scientific contributions concerning the role of cellular reprogramming, we conducted a bibliometric analysis encompassing literature from 2002 to 2022. This innovative approach offers a unique perspective that enables us to manage and depict knowledge structures in this specific area of research.

Between 2002 and 2022,global publications on cellular reprogramming in cancer research experienced a meteoric rise, especially after 2012,with China and the United States leading the surge as the top contributors. Despite China's higher publication count, the United States research garnered more citations, highlighting its significant impact. Significantly, the United States and China contributed 10 primary funding entities, underscoring the substantial investments made by both nations in this field. The distribution of the top 10 most prolific institutions further illuminated the global dynamics: 4 hailed from China, 6 from the United States, suggesting the critical role these nations play in advancing the field. Menendez stood out as a key author in the field. Among the top journals in the field, only three boasted an Impact Factor (IF) greater than 10.0: Nature Communications (IF2022, 16.6), Proceedings of the National Academy of Sciences of the United States of America (IF2022, 11.1), and Cancer Research (IF2022, 11.2), among others with Ifs between 5.0 and 10.0,guiding authors towards suitable publication venues for broader visibility.

4.2. The significant discoveries in cellular reprogramming in cancer

In 2008, DeBerardinis et al. proposed that cellular reprogramming in cancer significantly alters metabolic pathways to support tumor growth [25]. They noted that the metabolism of proliferating cells differs significant from that of non-proliferating ones emphasizing the important of pathways like aerobic glycolysis and lipid biosynthesis for cell proliferation. The study also touched on the regulatory roles of the PI3K/Akt/mTOR system and HIF-1 in cancer development, pointing towards potential therapeutic targets by understanding tumor metabolic complexity.

In 2011, Gaglio et al. highlighted the pivotal role of cellular reprogramming in cancer, driven by oncogenes like K-ras [26]. Using advanced techniques, they discovered that cells with oncogenic K-Ras show enhanced glycolytic activity and altered metabolism, emphasizing a shift in the tricarboxylic acid cycle. Notably, there is an increased reliance on glutamine for anabolic processes. This study underscores the significance of oncogenic K-Ras in metabolic reprogramming of cancer cells and provides a foundation for potential therapeutic approaches.

In 2013, Hu et al. discovered distinct metabolic gene expression in cancers compared to normal tissues, partly due to tumor-specific mutations [27]. Later that year, Son et al. then uncovered a unique glutamine metabolism in pancreatic ductal adenocarcinoma (PDAC) [28]linked to KRAS activation, deviating from conventional pathways. This finding on PDAC's metabolism reprogramming opens up new therapeutic possibilities targeting this specific pathway for PDAC treatment.

In 2018, Milanovic et al. studied the link between cellular senescence and cancer stemness, revealing how cancer cells can reprogram to become more aggressive after escaping senescence [29]. Their research in B-cell lymphomas showed that senescence increase stem cell traits in tumors, leading to a reprogramming state with enhanced tumor-initiating potential. This work highlights the critical role of cellular reprogramming in cancer progression and its implications for developing new therapeutic.

In 2021, Wang et al. identified cellular reprogramming as a key factor in cancer therapeutic resistance [30], highlighting the role of TIGAR, and interaction with NRF2 in resistant tumor cells. This interaction affects metabolism and epigenetics, enhancing tumor resistance and correlating with poorer patient outcomes.

4.3. The hotspots of cellular reprogramming in cancer

In this investigation, "cellular reprogramming" was highlighted as the most frequently cited term, while "immunotherapy" emerged as the most impactful keyword. Through co-occurrence analysis, the study underscored the critical role of cellular reprogramming in oncological treatments, particularly in its combined use with immunotherapy. Evidence suggests that cellular reprogramming can enhance the efficacy of T cells, thus strengthening anti-tumor immunity [31]. Additionally, prior research indicated that leveraging cellular reprogramming to convent cancer cells into antigen-presenting cells could potentiate specific T cells activation, leading to improved anti-tumor immune responses [32]. The study also examined the effects of cellular reprogramming on various cell populations within the tumor microenvironment [33]. The integration of cellular reprogramming with immunotherapy opens new pathways for research and holds promise for tailored cancer therapies [34]. While cellular reprogramming has ahieved some advances in immunotherapy, the exact mechanisms are still to be fully understood, calling for further investigation.

4.4. The mechanism of action of cellular reprogramming in cancer

To enhance our understanding of the variations in cellular reprogramming among different cancer types, and thereby guide clinical practice, we conducted a comprehensive analysis of the five most frequently keyworded cancer types. We compared the development of neoadjuvant immunotherapy for lung adenocarcinoma, pancreatic cancer, neuroblastoma, and papillary thyroid carcinoma. The varying degrees of progress in cellular reprogramming research pertaining to these specific categories of cancer have been clarified, along with the justification for these discrepancies.

Cellular metabolic reprogramming is crucial in breast cancer development, influencing glucose, amino acids, and lipids metabolism. Mutations in genes like p53 and PI3K alter glucose metabolism, while c-Myc overexpression promotes aerobic glycolysis and glutamine use [35]. Breast cancer subtypes show significant metabolic difference, including in glycolytic intermediates and lipid metabolism. Metastatic breast cancer cells adapt their metabolism [36] base on target sites, with those metastasizing to the liver converting glucose to lactate, a process linked to PDK1 crucial for liver metastasis. Understanding these metabolic alterations can help in early diagnosis and developing targeted therapies for breast cancer [37],highlighting the importance of metabolic pathways as potential treatment targets.

Cellular metabolic reprogramming is pivotal in the development of pancreatic cancer., Deubiquitylating enzymes (DUBs), notably USP25, are essential for tumor growth and sustainment by maintaining the stability of the transcription factor HIF-1α thereby impacting glycolysis within the tumor's core [38]. Additionally, a lack of MTAP enhances glycolysis and the synthesis of new purines, with studies associating MTAP deficiency with a glycolytic phenotype. The oncogenic KRAS gene plays a key role in pancreatic cancer initiation, influencing acinar-to-ductal metaplasia and PanIN formation through downstream pathways. These insights reveal numerous therapeutic targets and suggest novel treatment avenues for MTAP-deficient pancreatic cancer [39].

Cellular metabolic reprogramming,crucial in neuroblastoma, is largely influenced by MYCN amplification [40]. This genetic change significantly alters metabolic pathways, highlighting MYCN's role in the disease. The research emphasizes transcriptional regulation's importance in reprogramming and proposes metabolism-targeted treatments for high-risk neuroblastoma [41]. Specifically, inhibiting USP29,which stabilizes key metabolic regulators MYC and HIF1α, presents a novel therapeutic strategy, given the frequent deregulation of MYC and HIF1α in various cancers [42].

In papillary thyroid carcinoma (PTC). altered acid metabolism, notably through hydrolysis, transport, and oxidation, plays a key role [43]. Increased activity of enzymes like LPL, FATP2, and CPT1A correlates with PTC's aggressive behavior, advanced stages, and poor outcomes [44]. Additionally, higher LDHA levels, indicative of disrupted glucose metabolism, are linked to aggressive PTC features [45]. Understanding these metabolic shifts could clarify PTC's pathogenesis and highlight targets like LDHA for therapeutic intervention to slow tumor progression and enhance anti-tumor responses.

Cellular metabolic reprogramming is fundamental for the development of lung adenocarcinoma (LUAD). In LUAD, enzymes like PDK1 and LDHA are crucial for glucose metabolism and represent therapeutic targets [46], Genetic mutations in KRAS [47] and KEAP1 [48]influence glutamine metabolism, underscoring metabolic reprogramming's importance. The lncRNA FAM83A-AS1 [49], linked to glycolysis, also presents a potential target. Analyzing metabolic changes related to metastasis has identified new oncogenic drivers, suggesting that understanding these shifts could lead to novel LUAD treatment.

4.5. *The frontiers of cellular reprogramming in cancer*

The "burst detection" method in CiteSpace highlighting the keywords "tumor metabolism" [50] in 2022, points to the growing emphasis on cellular reprogramming in cancer research. Studies by Pavlova et al. delineated how tumorigenesis is intertwined with cellular metabolic reprogramming [51], triggered by oncogenic mutations. This reprogramming allows cancer cells to harvest essential nutrients from scarce environments, which are crucial for their survival and growth, and significantly affect gene expression, cellular differentiation, and the tumor microenvironment. Heiden et al. highlighted that transformed cells alter their metabolism to support tumor initiation and progression [52]. Understanding the specific metabolic pathways and preferences of malignant cells is key to developing more effective targeted metabolic therapies. Liberti et al. focused on metabolic rewiring in cancer cells, particularly the Warburg effect, emphasizing its role in tumor metabolism [53]. The keyword "tumor metabolism" underscores the importance of cellular reprogramming in cancer, with the research in 2022 shedding light on this crucial aspect. Elucidating the mechanisms underlying metabolic reprogramming may provide novel insights and therapeutic avenues for cancer treatment.

4.6. *Study limitations*

This study While bibliometric studies yield invaluable insights, it's important to acknowledge certain limitations inherent to this particular analysis. The primary constraint stems from the language selection criterion; focusing predominantly on English-language publications may inadvertently overlook significant contributions documented in other languages, potentially skewing the results. A more critical challenge lies in the data examination methodology. The intricacies of bibliometric analysis applications, coupled with occasional data export discrepancies, can introduce inconsistencies in the study outcomes. Additionally, editorial and typographical errors, particularly prevalent in older publications, further complicate the analysis. Such errors can lead to discrepancies in statistical data, especially concerning author names, which may vary due to different abbreviation conventions, name changes, institutional affiliations, or typographical mistakes. These issues present hurdles for analytical tools like VOSviewer.However, the increasing adoption of author identifiers like ORCID in recent publications is a promising development that could mitigate these challenges by providing a more reliable means of tracking authorship and contributions. Additionally, the potential delay in recognizing the impact of recently published high-quality studies due to citation lags warrants a cautious interpretation of current trends and necessitates ongoing re-evaluations in future analyses. Despite these constraints, the study offers valuable insights into the evolving landscape of cellular reprogramming in oncology, setting the stage for further exploration and innovation in personalized cancer treatment and metabolic therapies. Future research should aim to address these limitations by incorporating a broader spectrum of studies and employing methodologies to rapidly integrate new findings, thereby enriching our understanding and application of cellular reprogramming in cancer therapy.

5. Conclusion

In recent years, there has been a marked increase in the focus towards research on cellular reprogramming. The increasing number of publications underscores the burgeoning significance of this research area. This analysis delineates the frontrunners among researchers and institutions involved in cellular reprogramming research worldwide. "Cancers" emerged as the most vibrant journal, and Menendez JA was recognized as the most influential author. The nexus between cellular reprogramming and cancer metabolism is a sought-after topic. Moreover, the application of cellular reprogramming in immunotherapy is a pivotal area for future research. Therefore, this study provides a sweeping synopsis of the growth trajectory and the cutting-edge frontiers of this field for researchers and policymakers who are nascent to this domain.

Data availability statement

Data is available within the main text of the paper, provided as supplementary files, or cited directly in the document.

CRediT authorship contribution statement

Jinghao Liang: Formal analysis, Conceptualization. **Yijian Lin:** Software. **Yuanqing Liu:** Conceptualization. **Hongmiao Lin:** Supervision. **Zixian Xie:** Visualization. **Tongtong Wu:** Data curation. **Xinrong Zhang:** Project administration. **Xinyi Zhou:** Resources. **Zhaofeng Tan:** Formal analysis, Data curation. **Weiqiang Yin:** Methodology, Formal analysis. **Zhihua Guo:** Writing – review & editing, Visualization, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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