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SCIENTOMETRICS

Global research trends and prospects of cellular metabolism in colorectal cancer

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Abstract

BACKGROUND

An increasing number of studies have focused on the role of cellular metabolism in the development of colorectal cancer (CRC). However, no work is currently available to synthesize the field through bibliometrics.

AIM

To analyze the development in the field of "glucose metabolism" (GM), "amino acid metabolism" (AM), "lipid metabolism" (LM), and "nucleotide metabolism" (NM) in CRC by visualization.

METHODS

Articles within the abovementioned areas of GM, AM, LM and NM in CRC, which were published from January 1, 1991, to December 31, 2022, are retrieved from the Web of Science Core Collection and analyzed by CiteSpace 6.2.R4 and VOSviewer 1.6.19.

RESULTS

The field of LM in CRC presented the largest number of annual publications and the fastest increase in the last decade compared with the other three fields. Meanwhile, China and the United States were two of the most prominent contributors in these four areas. In addition, Gang Wang, Wei Jia, Maria Notar-nicola, and Cornelia Ulrich ranked first in publication numbers, while Jing-Yuan Fang, Senji Hirasawa, Wei Jia, and Charles Fuchs were the most cited authors on average in these four fields, respectively. "Gut microbiota" and "epithelial-mesenchymal transition" emerged as the newest burst words in GM, "gut

microbiota" was the latest outburst word in AM, "metastasis", "tumor microenvironment", "fatty acid metabolism", and "metabolic reprogramming" were the up-to-date outbreaking words in LM, while "epithelial-mesenchymal transition" and "apoptosis" were the most recently occurring words in NM.

CONCLUSION

Research in "cellular metabolism in CRC" is all the rage at the moment, and researchers are particularly interested in exploring the mechanism to explain the metabolic alterations in CRC. Targeting metabolic vulnerability appears to be a promising direction in CRC therapy.

Key Words: Cellular metabolism; Colorectal cancer; Glucose metabolism; Amino acid metabolism; Lipid metabolism; Nucleotide metabolism

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Core Tip: This paper performs a bibliometric analysis of the articles in the field of cellular metabolism in colorectal cancer (CRC). In detail, we first analyze the development and current status of this area, and finally explore the future development trend. In addition, we also summarize some hot topics on cellular metabolism in CRC, which will help researchers identify potential future research directions.

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INTRODUCTION

Colorectal cancer (CRC) is the 3rd most frequently diagnosed malignant tumor worldwide, while simultaneously having the 2nd highest mortality rate, imposing a significant disease burden worldwide[1]. Although significant progress has been made in treatment strategies for CRC, the prognosis of patients with CRC is still far from satisfactory[2].

Energy metabolism reprogramming is one of the most prominent hallmarks of cancer[3]. Research on cancer metabolism began approximately 100 years ago when Otto Warburg discovered that tumors produce lactic acid, known as aerobic glycolysis, even in the presence of sufficient oxygen, which we call the Warburg effect[4]. Compared to normal cells that produce adenosine triphosphate (ATP) for energy storage by oxidative phosphorylation through the tricarboxylic acid cycle (TCA cycle) under aerobic conditions, although glycolysis produces ATP much less efficiently, the production rate is much faster, which meets the material needs for rapid growth of cancer cells[5]. Glucose metabolism (GM) involves not only glycolysis but also other pathways that require glucose. Some of these include the pentose phosphate pathway (PPP), which produces pentose phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) for RNA synthesis, and the single-carbon metabolic cycle, which produces NADPH and is necessary for purine and glutathione biosynthesis, methylation, *etc*.[6]. Reprogramming of GM has been validated in many tumors by providing glycolytic intermediates as raw materials and thereby facilitating the biosynthesis of biomass such as amino acids, lipids, and nucleotides[7].

Numerous studies have revealed the important role of amino acids in cancer metabolism. In addition to being important fuels that support cancer development, amino acids also function in redox balance and homeostatic maintenance[8]. For example, glutamine supports the TCA cycle as a fuel by relinquishing the two amine groups[9]. In addition to glutamine, some branched-chain amino acids, such as valine, leucine, and isoleucine, can also provide fuel for the TCA cycle[10]. Additionally, glutamate, glycine and cysteine in cells mediate the redox balance by synthesizing glutathione, thus preventing cancer cell death[11-13]. Although NADPH from glycolysis and the PPP is usually considered to be a major contributor to redox homeostasis, NADPH produced by serine-derived single-carbon units driven by NADPH also makes a very important contribution[14].

Researchers have discovered early on the association of lipids with the etiology of cancer. In the 1960s, researchers revealed, through the detection of radiolabeled substrates, that the lipid metabolism (LM) of cancer cells was altered, as evidenced by the active synthesis and uptake of lipids[15]. In the mid-1990s, the connection between LM and cancer was prompted by the discovery of OA-519, an oncogenic antigen highly expressed in human breast cancer that encodes fatty acid synthase (FASN), a key enzyme involved in LM[16]. In addition, many studies have identified LM as one of the primary influences on tumorigenesis. Enhanced de novo synthesis of lipids mediated by upregulating the needed enzymes is considered to be a universal hallmark of tumorigenesis[17].

In the progression of tumors, the increased nitrogen demand of cells is considered one of the most important metabolic features, where nucleotides synthesized by proliferating cells are considered important molecules for maintaining proliferation in cancer[3], and nucleotide metabolism (NM) is considered to be the most critical aspect of tumorigenesis and cancer cell replication. First, the tumor microenvironment cannot provide sufficient amounts or nucleotide ratios unless

proliferating cells upregulate the integrative metabolism of nonessential amino acids, ribose, and single carbon donors to synthesize these complex molecules[18]. Second, cancer cells can utilize dysregulated NM to enhance proliferation and progression[19]. In addition, many oncogenic drivers have been shown to upregulate nucleotide biosynthesis, which is critical for cancer initiation and oncogene activation[20].

Bibliometrics is a branch of scientometrics in informatics. It functions as a quantitative analysis of patterns in the scientific literature to understand emerging trends and the structure of knowledge in a study field[21,22], which provides a quick reference guide for interdisciplinary researchers on how scientific experts evaluate the field[23]. Here, we visualized the trends and research hotspots in the field of "cellular metabolism in CRC" through bibliometric analysis so that researchers can obtain a more detailed understanding of the work in this area.

MATERIALS AND METHODS

Data acquisition

The topics "cellular metabolism in CRC", GM, AM, LM, and NM in CRC were searched on the Web of Science Core Collection (WOSCC). The search criteria were (TS=(metabolism)) AND TS=(colorectal cancer OR colorectal carcinoma), (TS=(glucose metabolism OR glycometabolism)) AND TS=(colorectal cancer OR colorectal carcinoma), (TS=(amino acid metabolism)) AND TS=(colorectal cancer OR colorectal carcinoma), (TS=(lipid metabolism OR fatty acid metabolism)) AND TS=(colorectal cancer OR colorectal carcinoma), (TS=(nucleotide metabolism)) AND TS=(colorectal cancer OR colorectal carcinoma), the time set to January 1, 1991 to December 31, 2022, the language set to English, and the article type set to research paper and review. The retrieved documents were saved in plain text format.

Data analyses

All of our analysis methods can be summarized as performance analysis and scientometric analysis. For performance analysis, we performed the analysis of annual publication data in CiteSpace 6.2.R4, and the analysis of country contribution was conducted in VOSviewer 1.6.19, while the cooperation between countries was performed on https://bibliometric.com/app. The scientometric analyses, including citation analysis, cocitation analysis, coauthorship analysis, bibliographic coupling analysis, and co-occurrence analysis, were all performed on VOSviewer 1.6.19, while the burst word analysis was performed on CiteSpace 6.2.R4. In addition, the analysis of keywords was performed after data cleansing.

RESULTS

Workflow and visualization analyses of research trends in annual publication volume

To analyze the trend of research concerning "cellular metabolism in CRC", we conducted a bibliometric analysis of the relevant documents published between 1991 and 2022, and the whole workflow is illustrated below (Figure 1A). From January 1, 1991, to December 31, 2022, a total of 7354 articles were published in the field of "metabolism in CRC", 903 articles in GM, 394 articles in amino acid metabolism (AM), 1398 articles in LM, and 497 articles in NM. Generally, articles concerning "cellular metabolism in CRC" showed a rising trend during this period, especially in the last decade (2012-2022), with a rapid outburst of articles, which exceeded more than three times the number of articles published a decade earlier (Figure 1B). Furthermore, documents on GM, AM, and LM in CRC presented a gradually increasing trend, especially on LM, which had the largest volume and fastest growth rate among these studies (Supplementary Table 1). However, the development of studies on NM was very limited, exhibiting a declining trend over the past four years (Figure 1C).

Contributions and cooperation from countries (regions) and institutions

We conducted a performance analysis to evaluate the contribution of different countries and organizations in the field of "cellular metabolism in CRC". The results of citation analyses suggested that 1347 institutions from 57 country regions contributed to the area of GM, 718 institutions from 50 countries contributed to the area of AM, 1884 organizations from 70 countries contributed to the area of LM, and 49 countries from 897 contributed to the area of NM. Notably, we found that China and the United States took the top two places in terms of publications in all fields (Figure 2), in which China ranked first in GM (318 papers), AM (129 papers), and LM (389 papers), while the United States ranked first in NM (167 papers) (Table 1). Meanwhile, in terms of the number of citations, the United States ranked first in all four areas, with 15929 citations in GM, 6754 citations in AM, 23819 citations in LM, and 7464 citations in NM (Table 1). For the average number of citations, Japan ranked first in AM (68 citations/paper) and NM (48 citations/paper) in CRC, while the United States ranked first in GM (83 citations/paper) and LM (63 citations/paper) (Table 1).

Concerning research institutions, all of them, apart from the German Cancer Research Center (German), were from China and the United States. Among them, Shanghai Jiao Tong University (China) ranked first in the number of publications in the fields of GM (36 papers), AM (14 papers), and LM (27 papers), while Fred Hutchinson Cancer Center (United States), German Cancer Research Center (German), and National Cancer Institute (United States) tied for first place in the field of NM (15 papers). Regarding citations, Shanghai Jiao Tong University (China) ranked first in GM (1518 citations) and LM (1863 citations), National Cancer Institute (United States) ranked first in AM (818 citations), and Fred Hutchinson Cancer Center (United States) ranked first in NM (689 citations) (Table 1).

Table 1 Top 5 countries and organizations with the highest number of publications related to cellular metabolism in colorectal cancer

Theme	Rank	Country	Publications/citations	Rank	Organizations	Publications/citations
Glucose metaboslim	1	China	318/7804	1	Shanghai Jiao Tong University (China)	36/1518
	2	United States	191/15929	2	Fudan University (China)	31/1052
	3	Germany	57/2864	3	China Medical University (China)	16/169
	4	Japan	56/2305	4	Sun Yat Sen University (China)	15/448
	5	Italy	54/3218	5	Chinese Academy of Science (China)	13/656
Amino acid metabolism	1	China	129/2431	1	Shanghai Jiao Tong University (China)	14/510
	2	United States	106/6754	2	Zhejiang University (China)	13/265
	3	Japan	38/2575	3	National Cancer Institute (United States)	13/818
	4	Germany	31/2053	4	Chinese Academy of Science (China)	10/170
	5	England	28/1024	5	Sun Yat Sen University (China)	10/348
Lipid metabolism	1	China	389/11486	1	Shanghai Jiao Tong University (China)	27/1863
	2	United States	376/23819	2	Sun Yat Sen University (China)	21/644
	3	Germany	93/3743	3	National Cancer Institute (United States)	20/1115
	4	England	87/4166	4	Fudan University (China)	19/1026
	5	Italy	80/4145	5	Central South University (China)	18/368
Nucleotide metabolism	1	United States	167/7464	1	Fred Hutchinson Cancer Center (United States)	15/689
	2	China	84/2166	2	German Cancer Research Center (Germany)	15/481
	3	Italy	51/1554	3	National Cancer Institute (United States)	15/572
	4	Germany	42/1358	4	Harvard University (United States)	10/486
	5	Japan	34/1647	5	Brigham and Women's Hospital (United States)	9/438

According to the coauthorship analysis, we found that China and the United States had the closest cooperation in the areas of GM, AM, and LM, while in the areas of NM, China, Germany, and Italy all had strong cooperation with the United States (Supplementary Figure 1). Overall, research on "cellular metabolism in CRC" spanned a wide range of work globally, and good partnerships between most countries facilitated advances in the field.

Analyses of journals and cocited journals

Another important indicator to track the development of a discipline is major publications and cocited journals. A total of 442 journals reported articles on GM, 233 journals reported articles on AM, 555 journals reported articles on LM, and 264 journals reported articles on NM. Meanwhile, 4538, 3158, 6480, and 3053 journals were cocited within these four areas respectively.

Then, we listed the top 10 journals in the field of "metabolism in CRC" by number of publications and cocitations. *Oncotarget* published the highest number of publications on GM (29 articles), while the *Journal of Nuclear Medicine* showed a much higher average number of citations than the other journals (112 citations/paper). *Cancers* ranked first in the number of publications on AM (11 papers) and LM (31 papers); additionally, *Cancer Research* (134 citations/paper) and *Scientific Reports* (52 citations/paper) ranked first in the average cited number within the above two areas. *Cancer Epidemiology Biomarkers & Prevention* issued the most publications on NM (21 papers), while *Cancer Research* had the highest average number of citations (142 citations/paper) (Supplementary Table 2).

Notably, *Cancer Research* had the highest number of cocitations in all four areas. We found that 87.5% of the top 10 journals in terms of publications were in Journal Citation Reports (JCR) Quartile in Category 2 (Q2) and above. In addition, 95% of the top 10 journals in terms of cocitations were in JCR Q2 and above (Supplementary Table 2). All of the above data illustrated the productive and high-quality results in the field of "metabolism in CRC", and the cocitation analysis also indicated that journals in different fields were relatively well connected, without any isolated journals (Figure 3).

Analyses of authors, cocited authors, and coauthorship authors

A total of 5826, 2599, 8436, and 3290 authors had outputs of articles in GM, AM, LM, and NM, respectively. Gang Wang

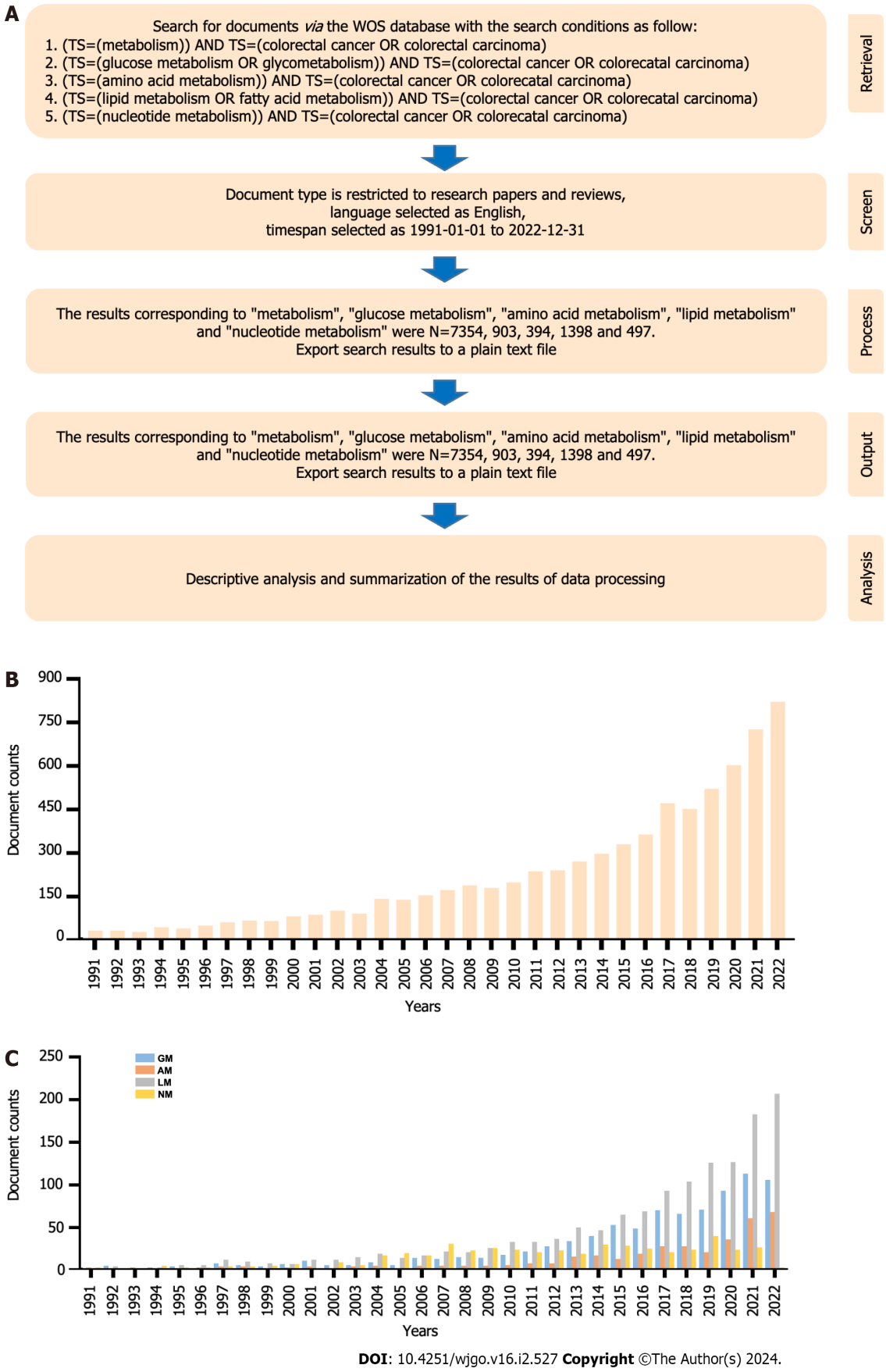

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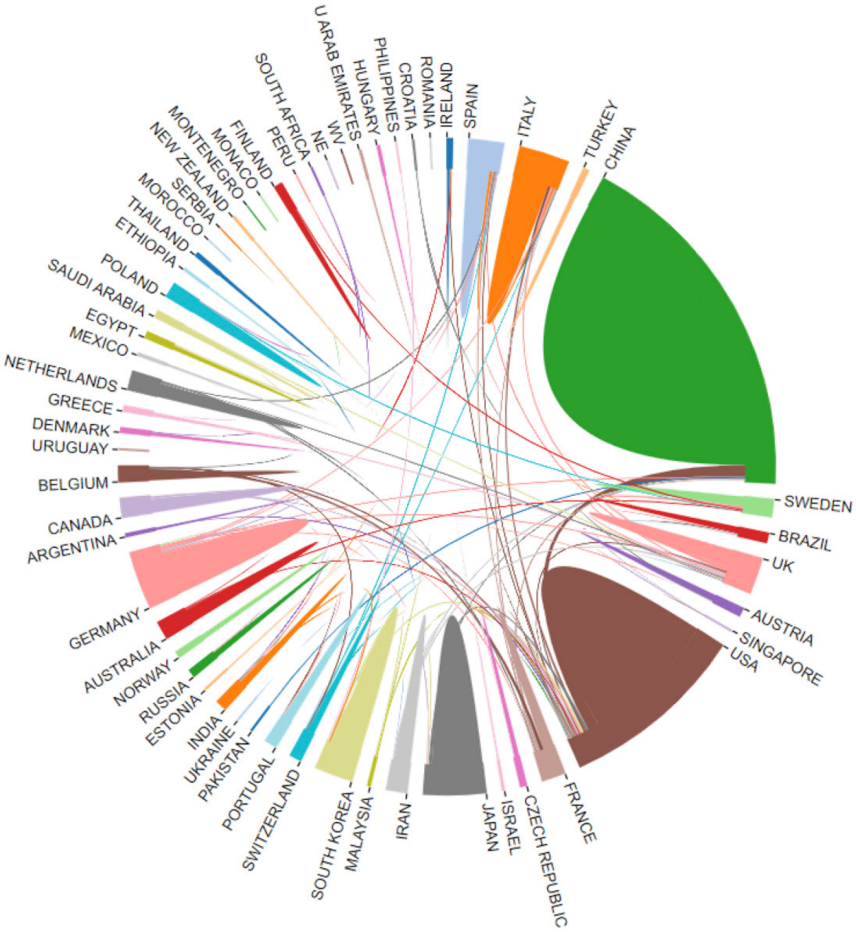
Figure 1 Workflow and annual publication analyses. A: Detailed process for searching subject terms in the Web of Science Core Collection (WOSCC); B: Annual number of publications in the field of "cellular metabolism in CRC" from 1991-2022; C: Annual number of publications in the fields of "glucose metabolism" (GM), "amino acid metabolism" (AM), "lipid metabolism" (LM), and "nucleotide metabolism" (NM).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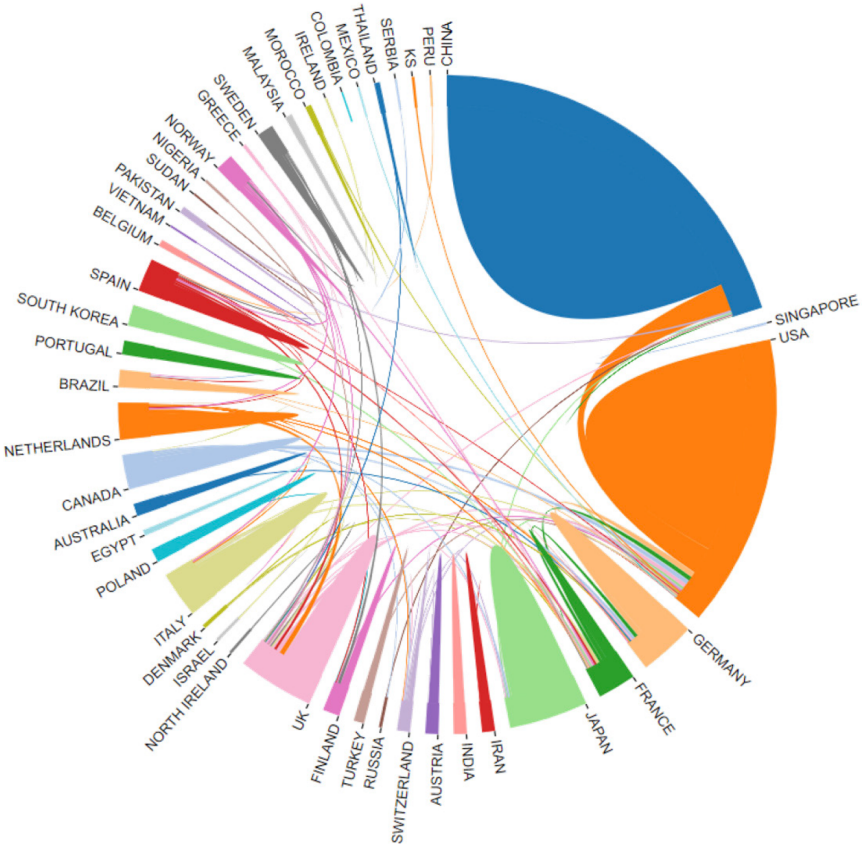
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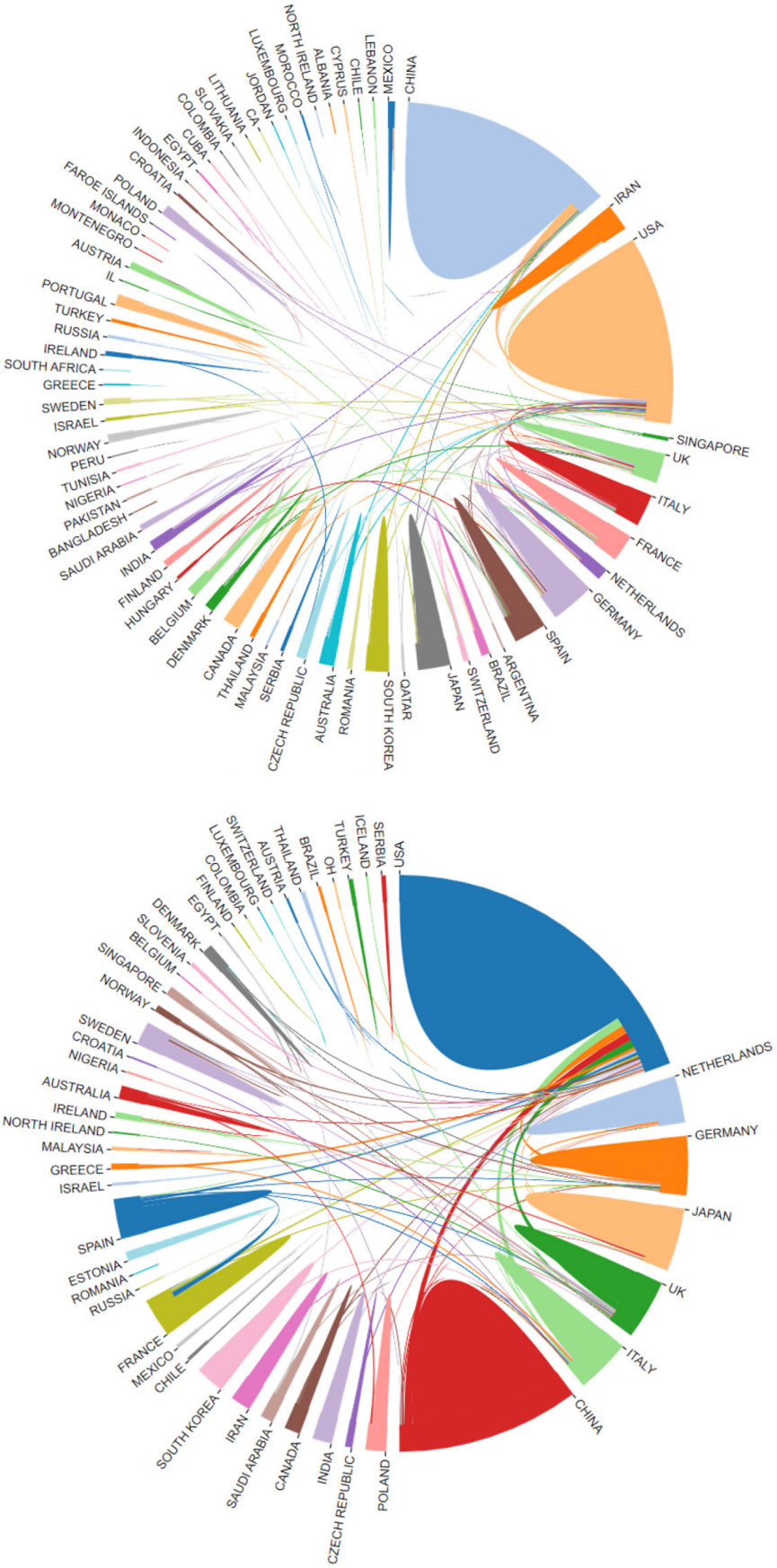

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Figure 2 Volume of publications and cooperation between different countries.

Table 2 Top 5 cited and cocited authors related to cellular metabolism in colorectal cancer

Theme	Rank	Author	Publications/citations	Rank	Cocited author	Publications/citations
Glucose metaboslim	1	Gang Wang	9/180	1	Otto Warburg	241/2009
	2	Zhuo-Yu Li	7/290	2	Matthew Vander Heiden	153/1409
	3	John Tayek	7/316	3	Douglas Hanahan	139/1106
	4	Yu-Zhu Wang	6/143	4	Ralph DeBerardinis	115/1291
	5	Jing-Yuan Fang	6/477	5	Gregg Semenza	107/979
Amino acid metabolism	1	Wei Jia	6/137	1	Ralph DeBerardinis	67/328
	2	Yoshiharu Sakai	5/208	2	Otto Warburg	61/243
	3	Kenji Kawada	4/196	3	Matthew Vander Heiden	42/202
	4	Kosuke Toda	4/196	4	Douglas Hanahan	39/127
	5	Senji Shirasawa	4/477	5	David R.Wise	37/169
Lipid metabolism	1	Maria Notarnicola	11/220	1	Douglas Hanahan	163/2712
	2	Valeria Tutino	10/200	2	Javier A. Menendez	151/2322
	3	Alois Kozubík	9/155	3	Bandaru S.Reddy	145/1992
	4	Ana Ramírez de Molina	9/377	4	Otto Warburg	143/2259
	5	Wei Jia	9/1325	5	Rebecca Siegel	124/1651
Nucleotide metabolism	1	Cornelia Ulrich	14/712	1	Cornelia Ulrich	136/1970
	2	Heinz-Josef Lenz	8/216	2	André van Kuilenburg	123/2054
	3	Giuseppe Toffoli	7/245	3	Jia Chen	96/1151
	4	Charles Fuchs	6/368	4	Young-In Kim	87/972
	5	Erika Cecchin	5/117	5	Koichi Kawakami	85/1611

had the highest number of publications in GM (9 papers), followed by Zhuo-Yu Li (7 papers) and John Tayek (7 papers), and Jing-Yuan Fang had the highest average number of citations (80 citations/paper) in this field. In the field of AM, Wei Jia produced the most publications (6 papers), followed by Yoshiharu Sakai (5 papers) and Kenji Kawada (4 papers), while Senji Shirasawa had a much higher average cited number (119 citations/papers) than the other authors. In the field of LM, Maria Notarnicola ranked first in the number of publications (11 papers), followed by Valeria Tutino (10 papers) and Alois Kozubík (9 papers), while Wei Jia ranked first in terms of the average number of citations (147 citations/paper). Cornelia Ulrich had the most publications (14 papers) in NM, followed by Heinz-Josef Lenz (8 papers) and Giuseppe Toffoli (7 papers), while Charles Fuchs was cited the most times per article (61 citations/paper) (Table 2).

Through the cocitation analysis, we found that the most cocited author in the field of GM was Otto Warburg (2009 times), followed by Matthew Vander Heiden (1409 times), Douglas Hanahan (1106 times) and others. Ralph DeBerardinis was the most cocited author in the field of AM (328 times), followed by Otto Warburg (243 times) and Matthew Vander Heiden (202 times). In the field of LM, Douglas Hanahan ranked first (2712 times), followed by Javier A. Menendez (2322 times), and Bandaru S. Reddy (1992 times). In the field of NM, Cornelia Ulrich was cited 1970 times, followed by André van Kuilenburg (2054 times), and Jia Chen (1151 times) (Table 2). Bibliographic coupling analysis showed that significant research directions were formed within all fields, and the links between authors were relatively tight, except John Tayek *et al* in GM, whose research directions had little connection to others (Figure 4). In contrast, the coauthorship analysis showed that collaborative relationships between authors were generally relatively decentralized (Supplementary Figure 2).

Analyses of key documents and cocited references

The key literature was the milestone in the development of a discipline. We showed the top ten cited articles in the four fields, where in GM, "Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice" was the most cited document with 1214 citations. "Serine, glycine and one-carbon units: cancer metabolism in a full circle", which was cited 983 times, was the most cited article simultaneously in AM and NM. The most cited document in the field of LM was "The gut microbiota, bacterial metabolites and colorectal cancer", which was cited 1571 times (Supplementary Table 3).

Cocited references are defined as documents that are cited by two or more documents simultaneously. The most cocited reference, "Understanding the Warburg effect: the metabolic requirements of cell proliferation" was the most cocited document in the field of GM (147 times) and AM (39 times). "Hallmarks of cancer: the next generation" was the most cocited document in LM (133 times). "A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase" was the most cited document in NM (44 times) (Supplementary Table 4).

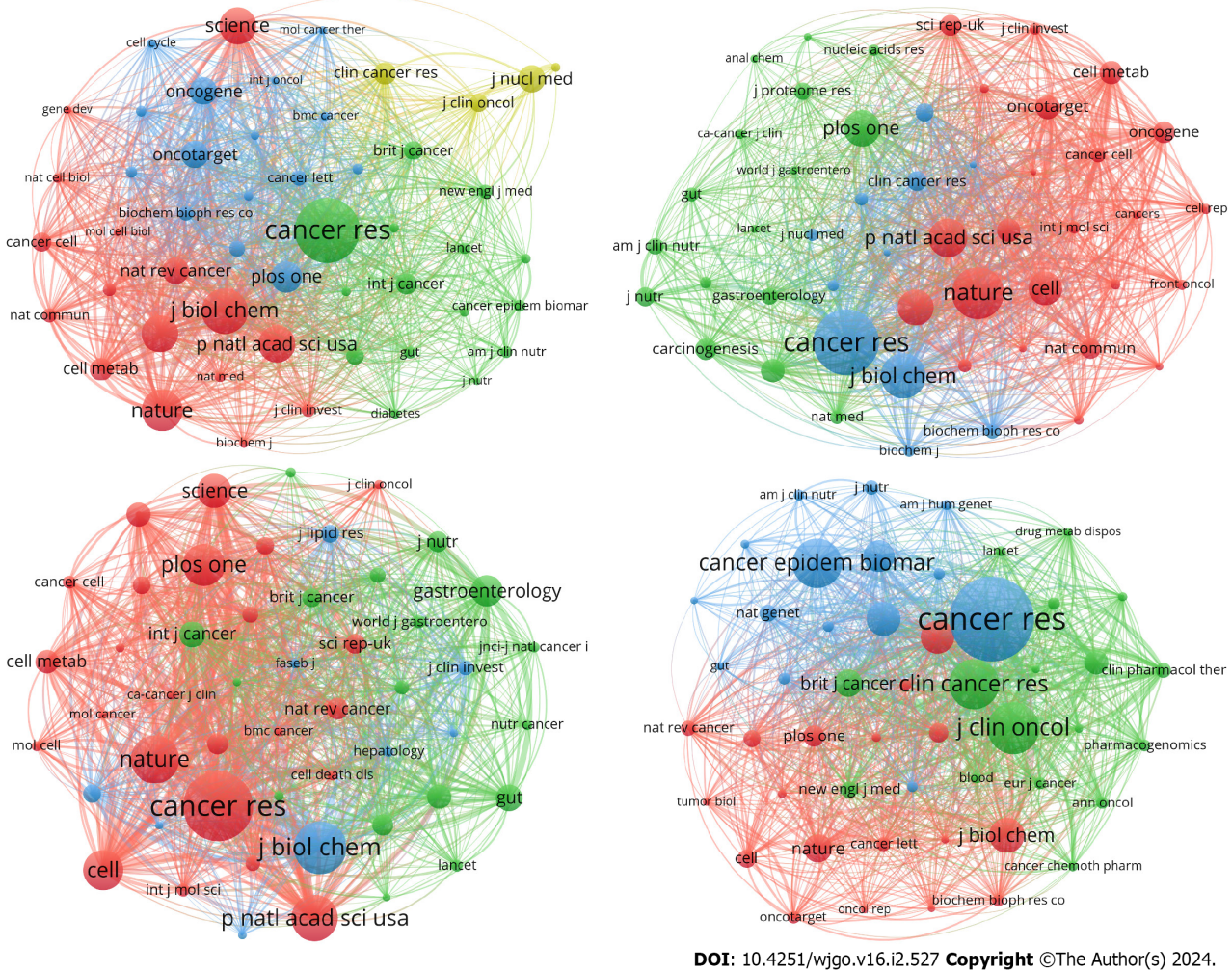

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Figure 3 Co-citation intensity analyses of journals.

Hotspots and forefronts

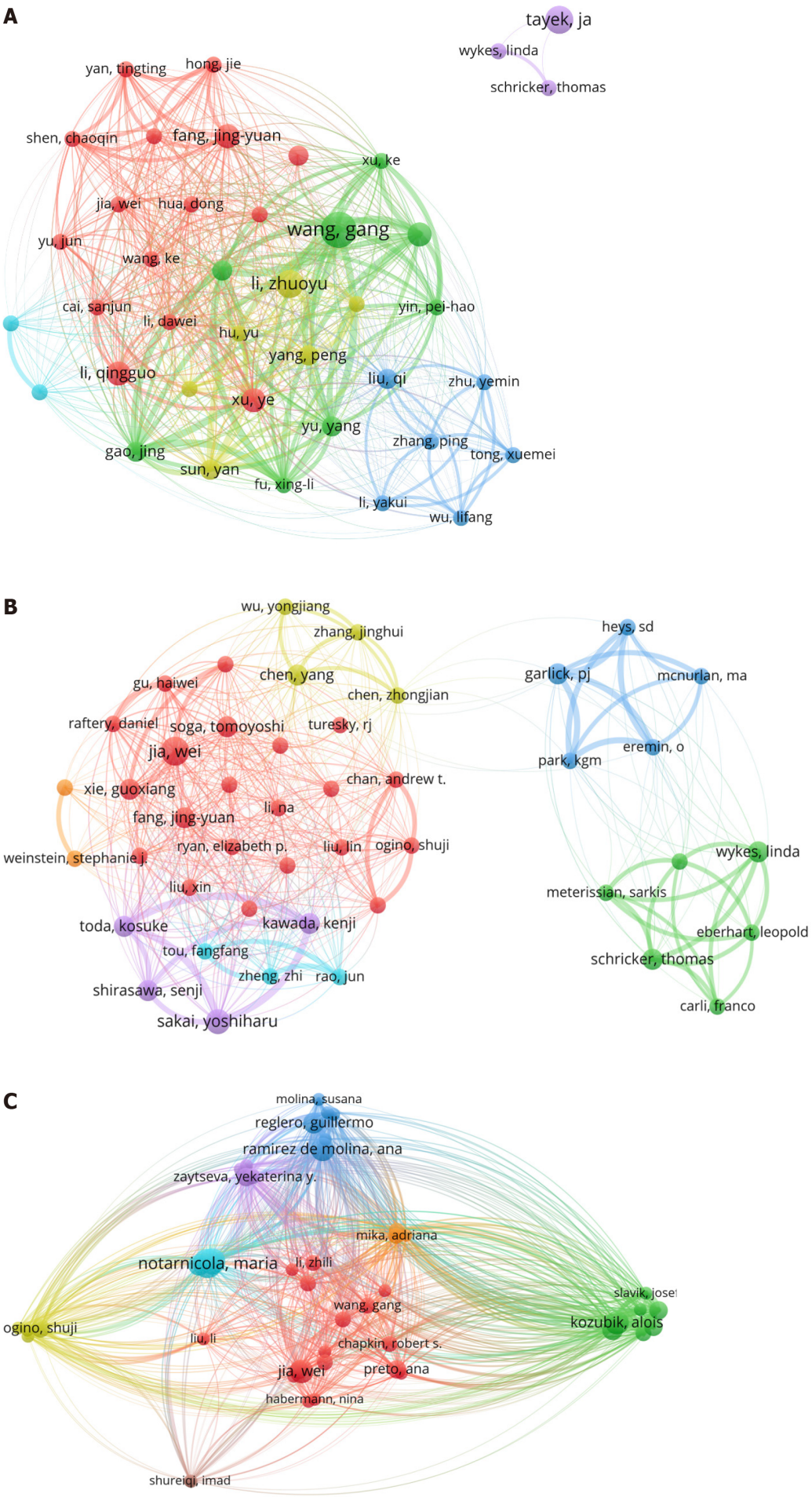
Analyses of occurring keywords and burst words assist us in identifying the research hotspots and trends in the development of a discipline. From the results of the most occurring words, we found that terms concerning aerobic glycolysis occupied the most position of the analyses in GM. In contrast, the keywords in the area of AM were more thematically dispersed; nonetheless, we found that glutamine metabolism was the most mentioned among all the kinds of AM. In LM, we concluded that terms including fatty acids were referred to most of the time. In addition, the lexicon on 5-FU chemotherapy-related processes in CRC was of greatest interest in NM (Supplementary Table 5).

We finally showed the burst words in different fields from 1991 to 2022. As was shown in the field of "metabolism in CRC", the burst words at the forefront were "tumor microenvironment" and "gut microbiota". In the field of GM, the present burst words were "gut microbiota" and "epithelial mesenchymal transition". The latest burst word was "gut microbiota" in the field of AM. In the field of LM, the up-to-date burst words were "metastasis", "tumor microenvironment", "fatty acid metabolism", and "metabolic reprogramming". In the field of NM, the most advanced burst words were "epithelial mesenchymal transition" and "apoptosis" (Figure 5).

DISCUSSION

Keeping track of research hotspots and staying abreast of the latest findings are essential for researchers. Therefore, scholars are required to be equipped with bibliographic retrieval and knowledge management. Bibliometrics is a cross science with the advantage of summarizing developments in specialized research areas and analyzing research hotspots [24]. We first summarize papers concerning "cellular metabolism in CRC" by means of bibliometrics, revealing the development in this discipline and predicting research hotspots in the future.

Generally, the development of research on "cellular metabolism in CRC" showed an upward trend. In particular, the most attention and investment of researchers was attracted in "LM in CRC". We assume that such a boom in the study of lipid metabolism in CRC is due to the development of effective tools for lipid measurements, including mass spectrometry-based lipidomics, which is making lipids a central role in cancer biology[17]. In addition, China and the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notarnicola, maria
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wang, gang
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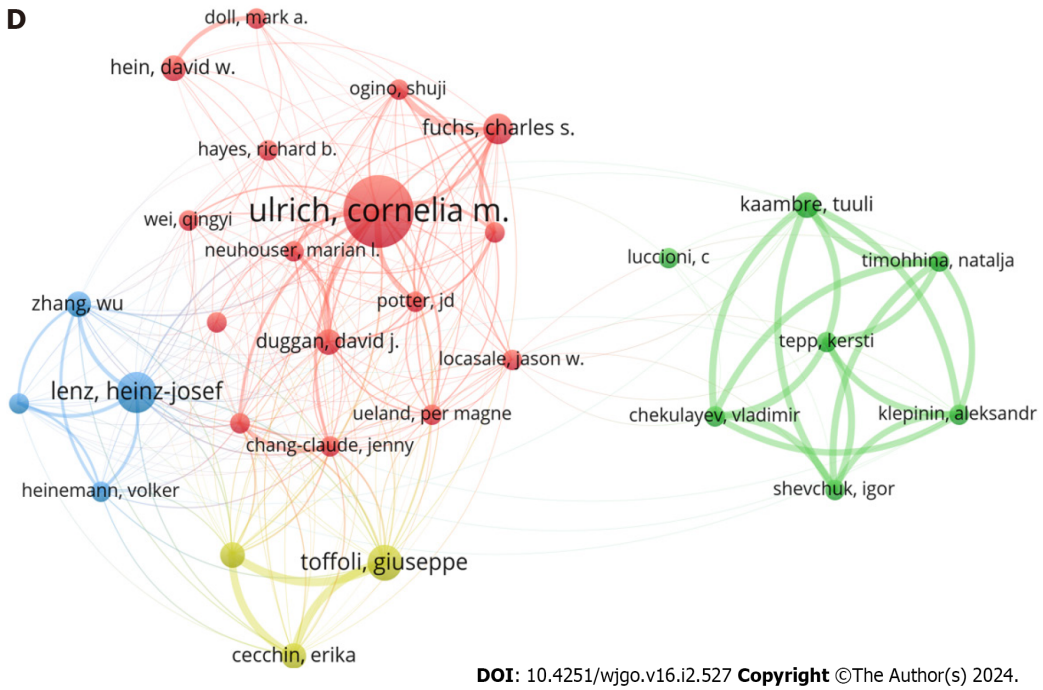

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Figure 4 Bibliographic coupling analyses of authors.

United States not only had the largest outputs, but also cooperated tightly with each other and promoted most of the inter-country cooperation in the four areas.

In detail, scientific mapping can help us quantify the structure of the research. As we can see in the analyses of the keywords (Supplementary Table 5), "Aerobic glycolysis", "Glycolysis", and "Warburg effect" are all contained in the frequently co-occurring words, which suggests that the glycolytic process is one of the most important directions in GM research. Numerous studies have reported that HK2, which catalyzes the first irreversible step in glycolysis, is upregulated in CRC and contributes to CRC progression. For instance, Yan *et al*[25] found that lncSLCC1 activated the expression of HK2 promoting tumor growth. Similarly, Shen *et al*[26] also showed that methyltransferase-like 3 stabilized HK2 and activated the glycolytic pathway, which in turn promoted tumor progression. It is noteworthy that all the articles cited above have the participation of Dr. Jing-Yuan Fang, which is consistent with the results of high-output authors in GM that we analyzed.

Our analyses of outbreak terms suggest that research on "gut microbiota" has recently become popular in GM. Enolase 1 (ENO 1) promotes the formation of phosphoenolpyruvate through the catalysis of 2-phosphoglycerate and the production of ATP during glycolysis[27]. *Fusobacterium* (F.) nucleatum promoted the expression of ENO 1 by upregulating the transcription of the lncRNA enolase1-intronic transcript 1 (ENO1-IT1), which induced glycolysis and oncogenesis in CRC cells[28]. Many studies have reported the role of glycolytic enzymes in the development of CRC, suggesting that in-depth research on glucose metabolism may provide new ideas for the treatment of CRC.

AM also plays an important role in the development of CRC[29]. For instance, serine-glycine-one-carbon metabolism, glutamine metabolism, *etc.*, have all been reported to participate in the bioprocesses of CRC[30,31]. Phosphoglycerate dehydrogenase (PHGDH) is a key enzyme that catalyzes serine biosynthesis by shifting the flux of glycolysis through the catalytic production of serine. Our previous study proved that PHGDH expression in CRC cells could be restored by hsa_circ_0062682, which ultimately promoted serine metabolism and tumor growth in CRC[32]. Likewise, Pan *et al*[33] recently revealed that PHGDH can serve as a novel substrate for GSK3β/FBXW7β, and that eIF3f can enhance the serine one-carbon metabolic pathway to promote CRC progression by deubiquitinating PHGDH. In contrast, increased alcohol dehydrogenase 1C was found to reduce serine levels by simultaneously inhibiting the expression of PHGDH, thereby inhibiting the growth, migration, and invasion of CRC cells[34].

As we mentioned before, with advances in technology, LM has become more concentrated as a process that converts nutrients into metabolic intermediates for energy storage and generation of the signaling molecules in CRC. FAs, which are the principal constituents of lipids[35], appeared in the most frequently occurring and outbreak words simultaneously. It should be mentioned that FASN, which emerged as the latest buzzword, utilizes acetyl-CoA and malonyl-CoA to resynthesize FAs. Wei *et al*[36] reported that COP9 signalosome subunit 6 (CSN6) and the tumor suppressor F-box and WD repeat domain-containing 7 (FBXW7β) prevented the degradation of FASN; as a result, the CSN6-FASN axis eventually promoted lipogenesis and tumor growth. Likewise, FASN could be restored by the deubiquitinase ubiquitin-specific protease 22, resulting in accelerated lipid synthase and tumorigenesis[37]. In addition, the upregulation of FASN also induces metastasis and oxaliplatin resistance in CRC[38,39]. Instead, inhibition of FASN diminished CD44 expression, which overwhelmingly restricted hepatic metastasis in CRC[39]. The antitumor activity of FASN attaches great significance in its prospect of being a promising therapeutic strategy for CRC. Intriguingly, Ye *et al*[40] recently found that fatty acid-binding protein 5 degrades FASN; however, this process ultimately promotes lipid accumulation

A **Top20 keywords with the strongest citation bursts**

Keywords	Strength	Begin	End	1991-2022
5 fluorouracil	29.91	1991	2008	
Fluorouracil	29.81	1991	2006	
Randomized trail	18.52	1991	2010	
Advanced colorectal cancer	21.77	1996	2014	
Susceptiblity	16.52	1997	2012	
Nonsteroidal antiinflammatory drugs	28.71	1998	2014	
Dihydropyrimidine dehydrogenase	32.41	1999	2012	
Thymidine phosphorylase	26.28	1999	2012	
Common mutation	32.1	2000	2014	
Risk factor	16.97	2000	2013	
Thymidylate synthase	38.53	2001	2012	
Methyleneterahydrofolate reductase	30.31	2002	2015	
Microsatellite instability	21.45	2003	2012	
Dna methylation	15.69	2003	2014	
Genetic polymorphisms	20.47	2005	2016	
Single nucleotide polymorphism	17.19	2005	2015	
Dietary folate	16.85	2005	2012	
One carbon metabolism	24.7	2009	2014	
Tumor microenvironment	19.5	2019	2022	
Gut microbiota	29.2	2020	2022	

B **Top11 keywords with the strongest citation bursts**

Keywords	Strength	Begin	End	1991-2022
Total parental nutrition	3.95	1991	1995	
F18 fluorodeoxyglucose	8.16	1992	2005	
Growth hormone	5.45	1992	2002	
Positron emission tomography	14.54	1997	2014	
Fdg pet	5.75	1998	2013	
Computed tomography	5.27	1998	2013	
Insulin resistance	5.53	2006	2011	
Hypoxia	4.28	2011	2013	
Glycolysis	4.59	2015	2017	
Gut microbiota	4.25	2020	2022	
Epithelial mesenchymal transition	3.9	2020	2022	

C **Top3 keywords with the strongest citation bursts**

Keywords	Strength	Begin	End	1991-2022
Carcinoma	4.33	2003	2016	
Mass spectrometry	3.95	2014	2018	
Gut microbiota	3.68	2018	2022	

D **Top15 keywords with the strongest citation bursts**

Keywords	Strength	Begin	End	1991-2022
Carcinogenesis	3.87	1992	2004	
Arachidonic acid metabolism	4.81	1997	2011	
Dietary fiber	4.02	1997	2002	
Lipid peroxidation	7.7	1998	2014	
Aberrant crypt foci	8.72	1999	2012	
Nonsteroidal antiinflammatory drugs	11.03	2001	2013	
Polyunsaturated fatty acids	4	2004	2014	
Ppar gama	5.71	2007	2017	
Resistant starch	4.06	2011	2012	
Body mass index	3.97	2017	2019	
Biomarkers	4.78	2018	2019	
Metastasis	7.9	2020	2022	
Tumor microenvironment	6.28	2020	2022	
Fatty acid metabolism	4.41	2020	2022	
Metabolic reprogramming	3.88	2020	2022	

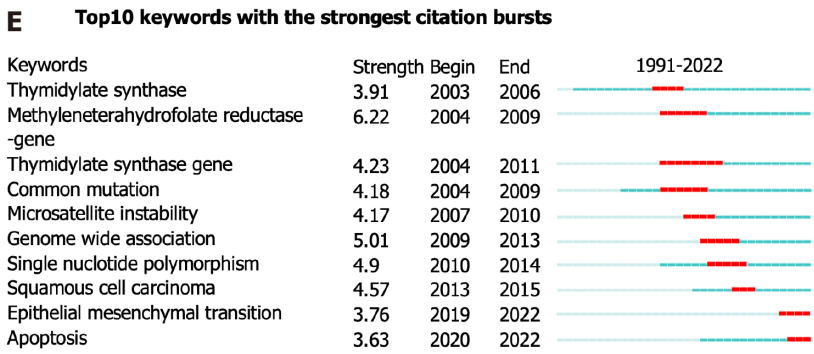

Figure 5 Burst words analyses from 1991-2022.

and inhibits mTOR signaling, which facilitates cell autophagy. Taken together, lipid metabolism, especially fatty acid metabolism, plays a fundamental role in CRC growth, metastasis and chemoresistance. Particularly, the study of FASN has recently drawn great interest from many researchers. Therefore, it is a meaningful exploration to target enzymes in CRC lipid metabolism for therapy.

Research in the area of NM has been quite sluggish in recent years, while the co-cited publications on "NM in CRC" were relatively independent of the other three fields. Specifically, the cocited literature mainly showed commonalities in studying the metabolic function of thymidylate synthase (TYMS) in CRC. Meanwhile, "5-fluorouracil", "thymidylate synthase" ranked the second and third respectively in the co-occurring keywords. To the best of our knowledge, TYMS, a folate-dependent essential enzyme that produces the sole intracellular source of dTMP needed for DNA synthesis and repair, is widely recognized as a target for the action of 5-FU[41].

Our study uses the WOSCC database for analyses of four principal areas in "cellular metabolism in CRC", while the setup of the parameters may not be completely comprehensive. For instance, researchers worldwide are going to deepen the study of cancer metabolism, while more branches of research are now being studied. Overall, we provide a comprehensive overview of the knowledge structure and outlook of the area of "cellular metabolism in CRC ".

CONCLUSION

This study presents the process of development in "cellular metabolism in CRC" between 1991 and 2022 as well as the current status through bibliometric analysis. The results showed that LM has the largest annual number of publications and growth rate, while NM has experienced a decline in recent years. China and the United States are the two largest contributors to all four fields, while the United States leads in the number of citations in all four areas. Correspondingly, research on "cellular metabolism in CRC" has very good cooperation among all countries. In terms of journals, 87.5% of the top 10 publications reach JCR Q2 and above, and 95% of the top 10 cocitation journals reach JCR Q2 and above. Moreover, the citation relationship among all journals is very tight. Although the citation relationship between articles is strong, it is not that close in author collaboration. In regard to key documents, many well-known reviews serve as references for these fields, especially in GM, AM, and LM, while the key references in the field of NM are relatively independent of the other three fields. Last, we notice that the foci of research in recent years have been more focused on the mechanism. In conclusion, this study suggests that research on "cellular metabolism in CRC" is all the rage currently, and researchers are interested in exploring the mechanism to explain the metabolic alterations in CRC. Targeting metabolic vulnerability appears to be a very promising direction for CRC therapy.

ARTICLE HIGHLIGHTS

Research background

An increasing number of studies have focused on the role of cellular metabolism in the development of colorectal cancer (CRC).

Research motivation

No work is currently available to synthesize the field through bibliometrics.

Research objectives

To analyze the development in the field of "glucose metabolism" (GM), "amino acid metabolism" (AM), "lipid metabolism" (LM), and "nucleotide metabolism" (NM) in CRC by visualization.

Research methods
Articles within the abovementioned areas of GM, AM, LM and NM in CRC, which were published from January 1, 1991, to December 31, 2022, are retrieved from the Web of Science Core Collection and analyzed by Citespace 6.2.R4 and VOSviewer 1.6.19.

Research results
The field of LM in CRC presented the largest number of annual publications and the fastest increase in the last decade compared with the other three fields. Meanwhile, cooperation within the countries and authors is also growing. Besides, the research on tumor metabolism in CRC is also gradually deepening the mechanism.

Research conclusions
Research in "cellular metabolism in CRC" is all the rage at the moment, and researchers are particularly interested in exploring the mechanism to explain the metabolic alterations in CRC. Targeting metabolic vulnerability appears to be a promising direction in CRC therapy.

Research perspectives
This study tells researchers that metabolic alteration in CRC is one of the most important hallmarks. Future research will not only expand in the four directions listed in the paper, but also produce many other branches and more refined metabolic types. At present, the research on lipid metabolism in CRC is very hot, which provides a future research direction for researchers to study the pathogenesis and development of CRC.

FOOTNOTES

Co-corresponding authors: Zhao-Hui Huang and Yan-Yan Chen.

Author contributions: Huang ZH and Chen YY determined the direction of this research; Liu YC analyzed data and wrote the draft; Huang ZH, Chen YY, Gong ZC, Li CQ and Teng P revised and checked the article.

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