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Research Hotspots and Trends in Global Cancer immunometabolism:A Bibliometric Analysis from 2000 to 2023

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Background: Cancer poses a major global health challenge, and immunotherapy, known as the third revolution in cancer treatment, has brought new hope to patients. The emerging field of immunometabolism has further enhanced the safety and efficacy of immunotherapy. Over the past two decades, this field has rapidly evolved in oncology, leading to numerous significant findings. This review systematically examines the literature on immunometabolism in cancer, visualizing research trends and identifying future directions.

Methods: A comprehensive literature search was conducted in the Web of Science, PubMed, and Scopus databases, covering publications from January 2000 to December 2023. We employed tools like Citespace, VOSviewer, and RStudio for visual analysis of publication trends, regional contributions, institutions, authors, journals, and keywords.

Results: A total of 3320 articles were published by 8090 authors across 1738 institutions, involving 71 countries. Leading contributors were China (n=469), the United States (n=361), and Germany (n=82). Harvard University was the most influential institution, while Frontiers in Immunology had the highest number of publications. The top research areas included glucose, lipid, and amino acid metabolism, the tumor microenvironment, and immune cell regulation.

Conclusion: International collaboration and interdisciplinary efforts are advancing the field of cancer immunometabolism. Future research will likely focus on the interplay between metabolism and immunity, metabolic markers, immune cell reprogramming, and tumor-immune metabolic competition.

Keywords: immunity, metabolism, tumor, metabolic reprogramming, immune evasion, bibliometrics

Introduction

Cancer remains one of the most pressing global health challenges. According to data from the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), approximately 19.29 million new cancer cases were reported worldwide in 2020, with about 9.96 million cancer-related deaths.[1] Notably, lung, breast, colorectal, prostate, and gastric cancers each had over one million new cases annually. By 2050, the global cancer incidence is projected to reach 35 million cases—a 77% increase from 20 million cases in 2022. Current cancer treatment strategies include surgical resection, radiotherapy, chemotherapy, targeted therapy, immunotherapy, hormone therapy, and gene therapy, often in combination to improve therapeutic outcomes. Supportive and palliative care also play key roles in symptom management and enhancing patients' quality of life.[2–4] Cancer immunotherapy was named "Breakthrough of the Year" by Science magazine in 2013, and in the past decade, it has made rapid advancements with significant breakthroughs in immune checkpoint inhibitors, CAR-T cell therapy, and NK cell therapy, among others.[5,6] However, despite its promise, tumor immunotherapy still faces numerous clinical challenges. One major hurdle is the heterogeneity of tumors, which results in variable patient responses and complicates the development of universal treatment regimens.[7] Moreover, immune responses are intricately linked with metabolic reprogramming. For example, acetate can reprogram

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tumor metabolism by upregulating c-Myc, promoting PD-L1 expression, and ultimately contributing to immune evasion.[8] On the other hand, acetate can also boost the antitumor activity of T cells and NK cells.[9] Therefore, a deeper exploration of immune metabolic mechanisms is essential to enhance immune surveillance and the efficacy of immunotherapies.

Immunometabolism, an emerging field, has shown significant promise in cancer treatment. As research progresses, growing attention is being directed towards understanding how immune cell metabolism influences their proliferation, activation, and maintenance of immunological memory.[10,11] The metabolic reprogramming of immune cells substantially impacts their function, and modulating metabolic pathways may enhance immune responses. For instance, memory T cells rely primarily on fatty acid oxidation to sustain their function, and metabolic regulation is crucial for T cell activation and the formation of immune memory.[12] During the process of tumor surveillance and eradication, immune cells must compete with cancer cells for nutrients and survival space.[13] Additionally, the metabolic byproducts of tumor cells create an immunosuppressive microenvironment, which weakens the ability of immune cells to effectively monitor and kill tumor cells, as illustrated in Figure 1. In response, some researchers have proposed investigating metabolic checkpoints, suggesting that metabolic regulation is a vital aspect of optimizing immune function.[14] Ongoing research aims to uncover ways to enhance antitumor immunity by modulating immune cell metabolism, including identifying and targeting specific metabolic pathways to improve immune cell performance in the tumor microenvironment.

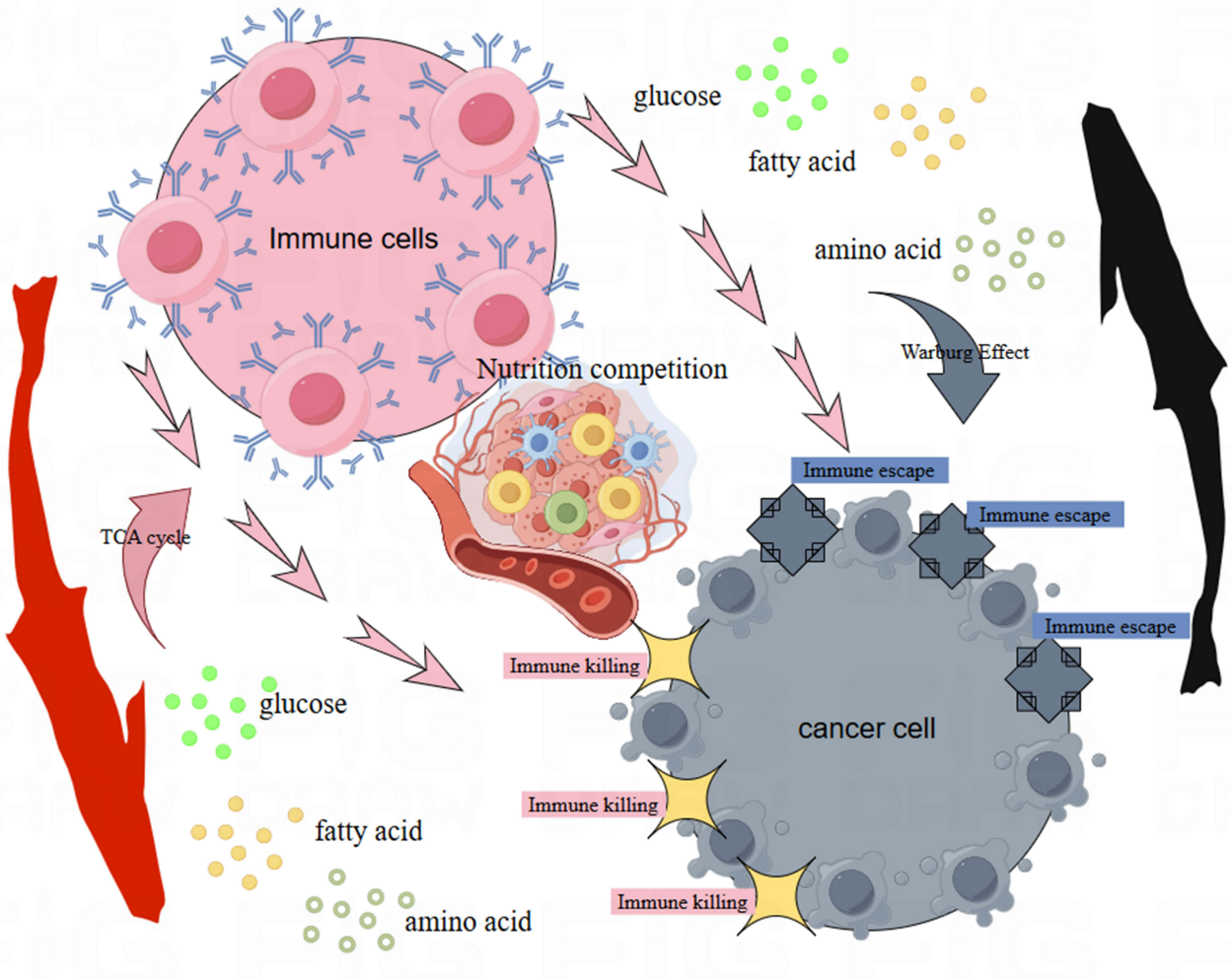

Figure 1 The nutritional competition between immune cells and tumor cells. Tumor cells undergo metabolic reprogramming under genetic regulation to meet their higher energy demands. Similarly, immune cells experience metabolic reprogramming in response to external stress stimuli. Tumor cells produce inhibitory substances through their metabolism to evade immune cell attacks while competing for more survival space and nutrients. Consequently, regulating immune metabolism is fundamental to maintaining homeostasis in the body.

Bibliometrics is a scientific discipline that employs mathematical and statistical techniques to analyze literature and assess trends in scientific research. It provides valuable insights into the dynamics of scientific progress, research hotspots, and interdisciplinary collaboration by evaluating the distribution, structure, and interconnections of scientific publications.[15] Bibliometric analysis assists researchers in assessing the impact of specific fields, identifying key journals and influential papers, and tracking networks of scientific collaboration. Visualization techniques further aid in presenting complex data in a clear and interpretable manner, allowing patterns and trends to emerge more readily.

This study aims to systematically review the literature on immunometabolism in cancer research from 2000 to 2023 using bibliometric and visualization techniques. By thoroughly exploring the landscape of research in this field, the study seeks to provide meaningful insights and valuable references to support future research, ultimately advancing precision oncology.

Materials and Methods

Data Source and Literature Search

The literature is sourced from the Web of Science Core Collection (WoSCC) database, Pubmed, and Scopus databases., and the search time was from 1 January 2000 to December 31, 2023. The search formula used was(((TS=("Carbohydrate Metabolism" OR "Lipid Metabolism" OR "Amino Acid Metabolism" OR "Nucleotide Metabolism" OR "Energy Metabolism" OR "TCA cycle")) AND TS=("Immunometabolism" OR "Intrinsic immunity" OR "adaptive immunity" OR "T cells" OR "B cells" OR "dendritic cells" OR "macrophages" OR "phagocytic cells" OR "natural killer cells")) AND TS=("cancer" OR "tumor" OR "neoplasm" OR "malignancy" OR "oncology" OR "hematologic malignancies" OR "blood cancer" OR "leukemia" OR "lymphoma" OR "multiple myeloma").

Data Screening

Inclusion Criteria

(1) Literature containing immune cells (innate and adaptive immunity); (2) Literature containing cancer cells, cancer, and various tumors; (3) Literature involving metabolites, including carbohydrate, lipid, and amino acid metabolism; (4) Literature published in English; (5) Literature types include clinical trial studies, in vitro experimental studies, in vivo experimental studies, public database analysis studies, reviews,etc; (6) Literature with complete bibliographic information (including title, country, author, keywords, source).

Exclusion Criteria

(1) Conference papers, newspapers, patents, achievements, health and popular science literature, etc.; (2) Duplicate publications; (3) The literature cannot be fully obtained.

The inclusion and exclusion process is independently conducted by two reviewers. If the inclusion and exclusion results are inconsistent, the third reviewer will participate in the work.

Data Standardization

After screening, the literature was exported in Refworks and plain text formats. Special symbols were removed. Keyword names were standardized, for example, "acute myelogenous leukemia" was merged into "acute myeloid leukemia". Country/Region names were standardized, for example, "North Ireland","Wales","England","Scotland" were determined as "United Kingdom". Then, the Data Import/Export function in CiteSpace software was used to convert the format of the retrieved literature.

Data Analysis

(1) Data Extraction

The normalized text data will be incorporated into a structured form designed by two researchers, who will then extract relevant data. The extracted data includes the following parts: publication information, encompassing the year of publication, country/region, issuing organization, issuing journal, authors, cited literature, and keywords.

(2) Analysis Methods

This study integrates multiple bibliometric visualization tools to thoroughly analyze and reveal critical insights in cancer immunometabolism research. CiteSpace was used to export and organize data, while Excel enabled the prediction of publication trends with fitting curves. VOSviewer played a key role in visualizing collaboration networks and geographic distribution, and its results were further enhanced using Tableau Public and Scimago Graphica for clearer regional and institutional patterns. RStudio, with the bibliometrix package, provided robust analysis of journals, authors, and citation networks. Pajek was utilized for mapping complex author collaboration networks and analyzing co-cited authors, offering a deeper understanding of research clusters. Carrot2 facilitated keyword clustering and topic evolution, helping to visualize emerging research trends. Together, these tools provided a comprehensive view of the field's development, contributing to an in-depth analysis of research hotspots and future directions, as illustrated in Figure 2.

Results

The Trends of Annual Publication and Citations

Figure 3A illustrates the changes in the number of research publications on immunometabolism in the field of oncology from 2000 to 2023. Based on the growth rate of publications, this period can be divided into three phases. From 2000 to 2010, the phase is characterized by slow growth, with a cumulative publication count of 190 articles and an average annual publication rate of 17.27 articles. This period represents the nascent stage of the discipline, primarily marked by exploratory research. The period from 2011 to 2016 is marked by steady growth, with a cumulative publication count of 520 articles and an average annual publication rate of 86.66 articles. This phase indicates increasing research interest and the construction of the theoretical framework of the discipline. From 2017 to 2023, the field experienced a rapid growth phase, with a cumulative publication count of 2438 articles and an average annual publication rate of 348.28 articles. This stage signifies the period of in-depth research, with higher attention and investment in the field. Additionally, to accurately predict future development trends, a polynomial fitting curve was plotted in Figure 3B. This curve shows that literature in this field is expected to grow explosively, with a coefficient of determination ($R^2 = 0.97$) indicating that the model explains 97% of the data variability, thus providing a highly valuable reference. The publication volume and citation data suggest that the interactions in immunometabolism are currently a focal point in oncology and that the field holds promising prospects for future development.

National and Regional Studies

Over the past 20 years, 71 countries/regions have participated in research on this project. Figure 4A illustrates the collaboration relationships among the top 30 countries in terms of publication volume, with the United States having the highest collaboration intensity at 225 international collaborations, followed by China with 103 collaborations, and Germany in third place with 100 international collaborations. Figure 4B depicts the annual publication trends over the past 20 years for the top 10 countries. The United States and Germany began publishing related literature in 2003, with the United States showing steady annual publication growth thereafter. Notably, post-2018, China, the United States, Germany, and other top 10 countries have shown stable growth in publication volume, suggesting that these countries/regions have established relatively stable research teams in this field. Figure 4C presents the geographical distribution of global publication volume, providing a clear visualization that most countries/regions worldwide are dedicated to research in this area. The upward arrows indicate countries with highly influential research in this field. Table 1 details the top countries in terms of publication volume, including specifics on Counts, H-index, Cooperation intensity, and Average citation per paper. The United States has the highest H-index at 95, with a total citation count of 31,238 and an average of 86.53 citations per paper. China follows with an H-index of 44, a total citation count of 9530, and an average of 21.27 citations per paper. From the regional distribution of the literature, it is evident that the role of immunometabolism in oncology has garnered global attention and holds significant influence.

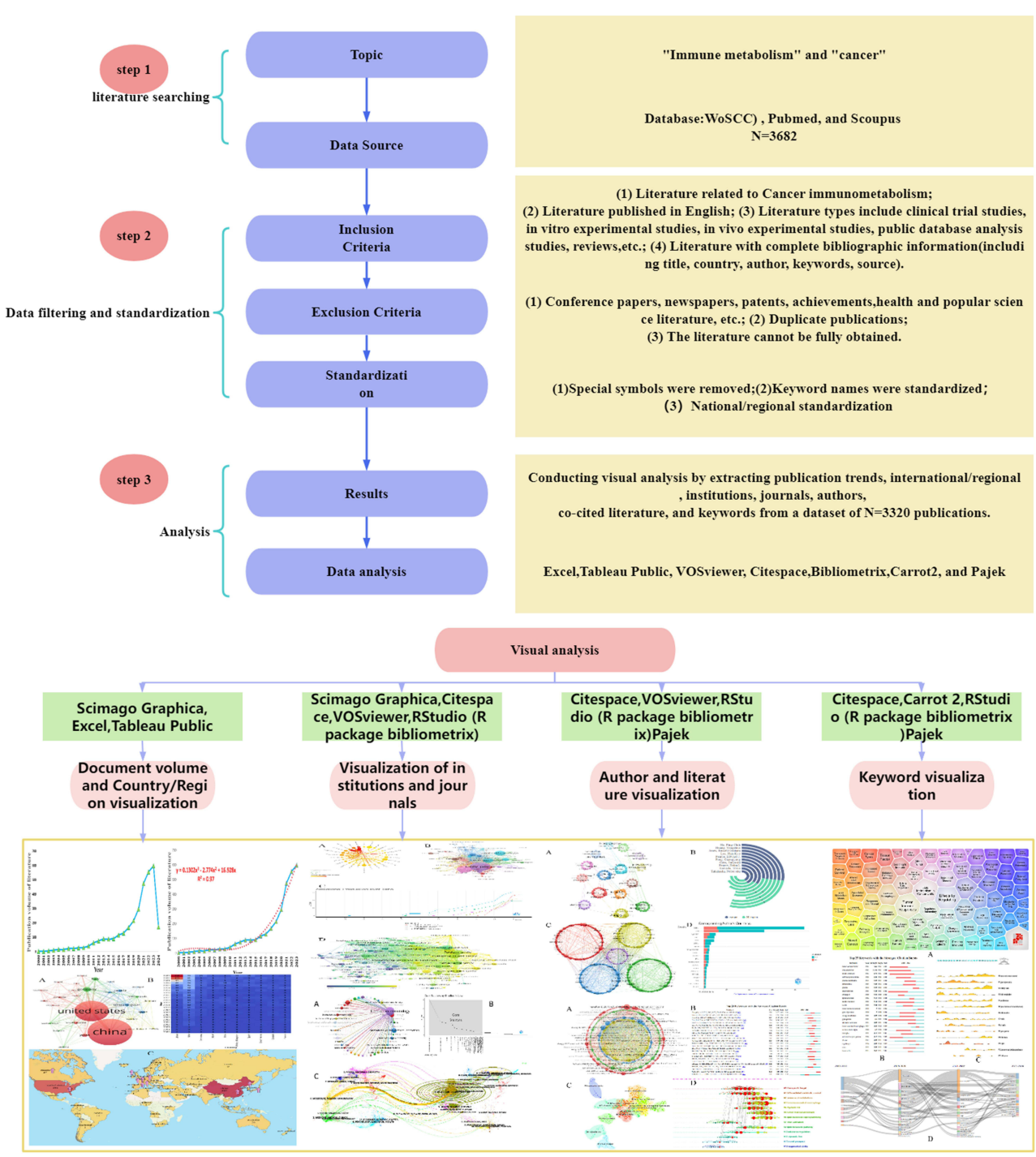

Figure 2 Visual analysis process of immune metabolism in the field of cancer research.

Analysis of Research Institutions

A total of 1738 institutions participated in this study. As shown in Figure 5A and Table 2, Harvard University had the highest number of publications, with 62 papers, followed by Central South University with 55 papers, and the Chinese Academy of Sciences with 44 papers. The Chinese Academy of Sciences, Harvard Medical School (HMS), and Karolinska Institutet were the institutions with the highest collaboration intensity. The University of Pennsylvania was the most cited institution with 4336 citations, followed by McGill University with 3392 citations and the University of

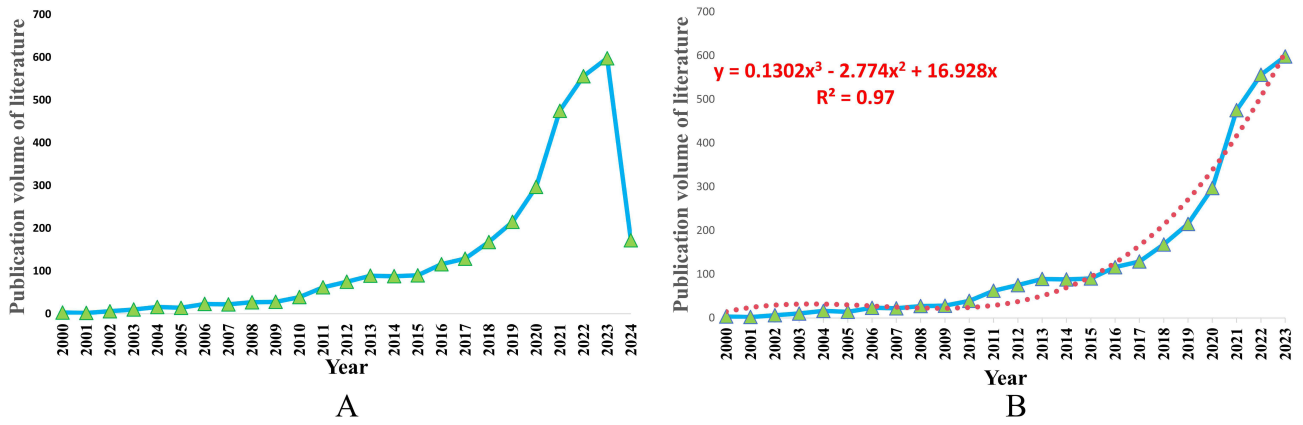

Figure 3 Annual publication volume and trend of research on immune metabolism in the field of tumors; (**A**) shows the annual publication volume, and (**B**) shows the development trend. According to the annual publication volume and polynomial analysis of tumor immune metabolism, there have been over 100 studies per year since 2016, and the number is rapidly increasing.

California, San Diego with 2389 citations, as depicted in Figure 5B. The annual publication volume of the top five institutions is displayed in Figure 5C. Over the past 20 years, Harvard University has maintained a leading position in publication volume in this field, indicating that Harvard University is a leader in the development of this domain and a center for knowledge innovation and dissemination. Harvard University, Central South University, Chinese Academy of Sciences, Nanjing Medical University, and Harvard Medical School are projected to produce more than 40 publications annually after 2023, suggesting that these institutions have entered a new phase of research on immunometabolism in oncology. The visualization of institutional bibliographic coupling provides a clear view of the collaborative relationships between different research institutions. High coupling strength between institutions indicates a significant number of shared citations, often reflecting collaboration in research projects or fields. In 2016, the University of Pennsylvania had the highest coupling degree and was at the core of the network. After 2020, the coupling degree among various institutions has increased, with Harvard Medical School (USA), Nanjing Medical University (China), and Sun Yat-sen University (China) actively engaging in international collaboration, as shown in Figure 5D. The increase in coupling degrees among institutions suggests more frequent collaboration, knowledge sharing, and interdisciplinary integration in this field, indicating that research in this area is maturing.

Journals and Co-Cited Journals

Over the past 20 years, 509 journals have reported on research in this field. Among them, *Frontiers in Immunology* had the highest number of publications, with 80 articles, as shown in Figure 6A and Table 3. *Cell Metabolism* had the highest impact factor (29.0). Additionally, *Frontiers in Immunology* had the highest H-index (22), followed by *Cell Metabolism* (13) and the *International Journal of Molecular Sciences* (12), as seen in Table 3. According to Bradford's law, the following 29 core journals were identified, with *Frontiers in Immunology, International Journal of Molecular Sciences, Cancers*, and *Frontiers in Oncology* scoring over 20, as shown in Figure 6B. The dual-map overlay of journals displays the citation relationships between citing and cited journals. On the left, the citing journal clusters represent the distribution of the knowledge frontier in this field, while the cited journal clusters on the right represent the important knowledge base of this field. As shown in Figure 6C, the orange paths indicate that journals from fields such as Molecular, Biology, and Genetics are most likely to be cited by journals focusing on Molecular, Biology, and Immunology, suggesting that the latest research includes many interdisciplinary studies. Simultaneously, the green paths indicate that literature from topics such as Molecular, Biology, Genetics, Health, Nursing, Medicine, Psychology, Education, and Social Sciences are most likely to be cited by journals related to Medicine, Medical, and Clinical themes. This implies that the field is characterized by multidisciplinary intersection and integration.

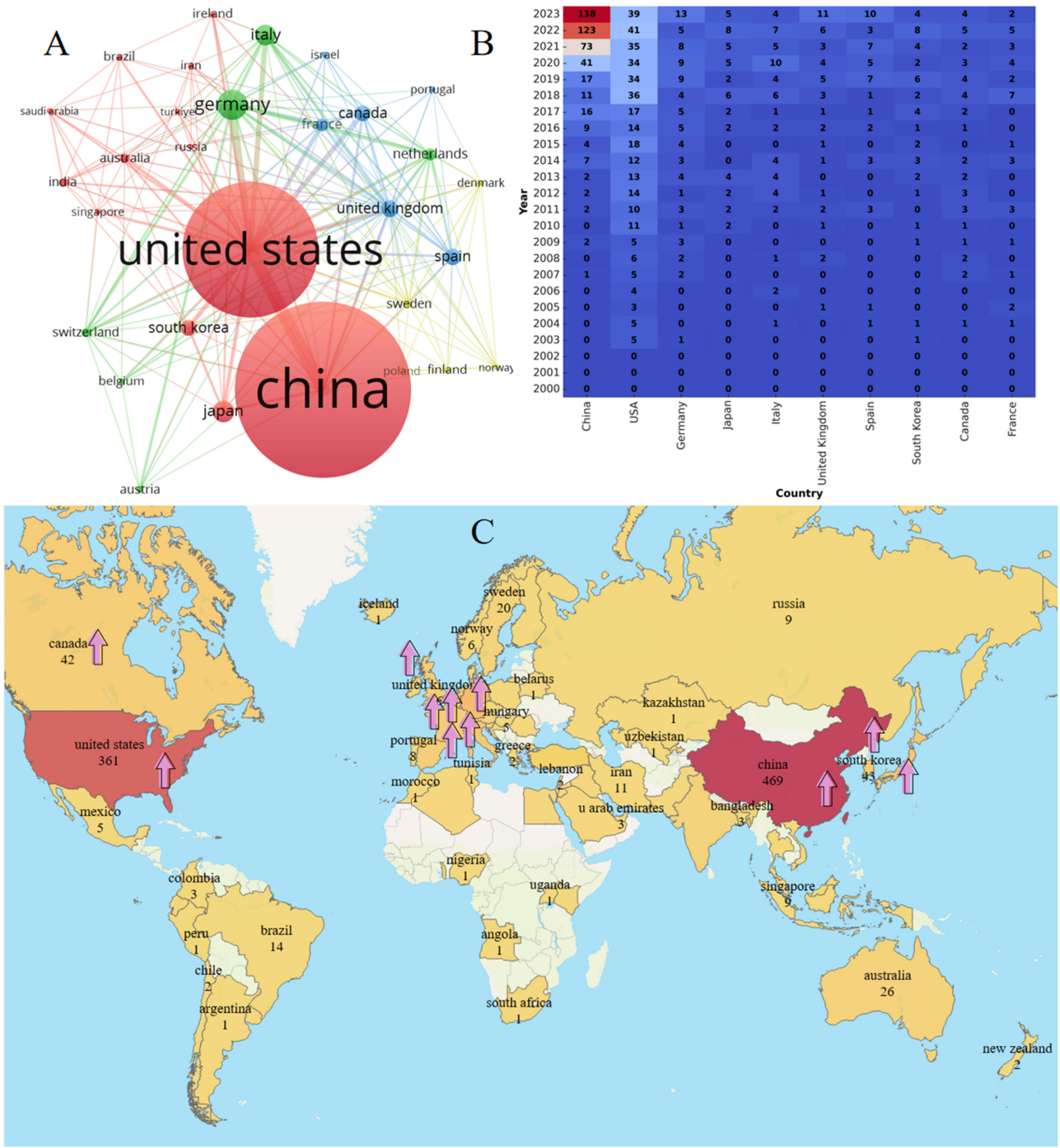

Figure 4 Visual analysis of countries/regions. (**A**) National/Regional Cooperation Network, (**B**) Top 10 Countries/Regions Annual Publication Heat Map, (**C**) Global Geographical Distribution of Immune Metabolism in Cancer Research, ↑ represents a high H-index.

Authors and Co-Cited Authors

A total of 8090 authors have contributed to research in this field, with 15,500 cited authors. According to the Price's Law formula Mp=0.749 * √ NPmax (core author publication volume>Mp), N=6 and Mp=1.83 are determined. Therefore, a publication volume of ≥ 2 is designated as the core author of the literature, and this study has 513 core authors. As time progresses, more core authors have formed relatively stable research teams. The emergence of these core teams is not only an important indicator of the maturation and development of the research field but also a key force driving scientific

Table 1 The Number of Publications and Citations in the Top 10 Countries/Regions

Rank	Country	Counts	H-index	Cooperation Intensity	Average Citation Per Paper
1	China	469	44	103	21.27
2	United States	361	81	225	86.53
3	Germany	82	31	100	75.55
4	Japan	58	26	27	43.55
5	Italy	57	27	49	62.6
6	United Kingdom	46	23	85	81.15
7	Spain	44	20	35	27.68
8	South Korea	43	22	24	37.84
9	Canada	42	20	38	130.64
10	France	35	18	43	37.31

progress and technological innovation. Currently, 15 relatively stable research teams have been formed, as shown in Figure 7A. The H-index is a metric used to evaluate the impact of a researcher's academic contributions, reflecting both the number of papers published and their citation impact. During this period, Takahashi Nobuyuki, Kawada Teruo, and Pearce Erika L have the highest H-index (H = 5), as shown in Figure 7B. Co-cited author analysis helps identify influential researchers in a specific research field, who are often thought leaders or key innovators. Chang Ch (n = 154) is the most frequently co-cited author, followed by Zhang Y (n = 147) and Hanahan D (n = 142). Furthermore, co-cited authors form five clusters, indicating at least five research themes and domain divisions within this field, as shown in

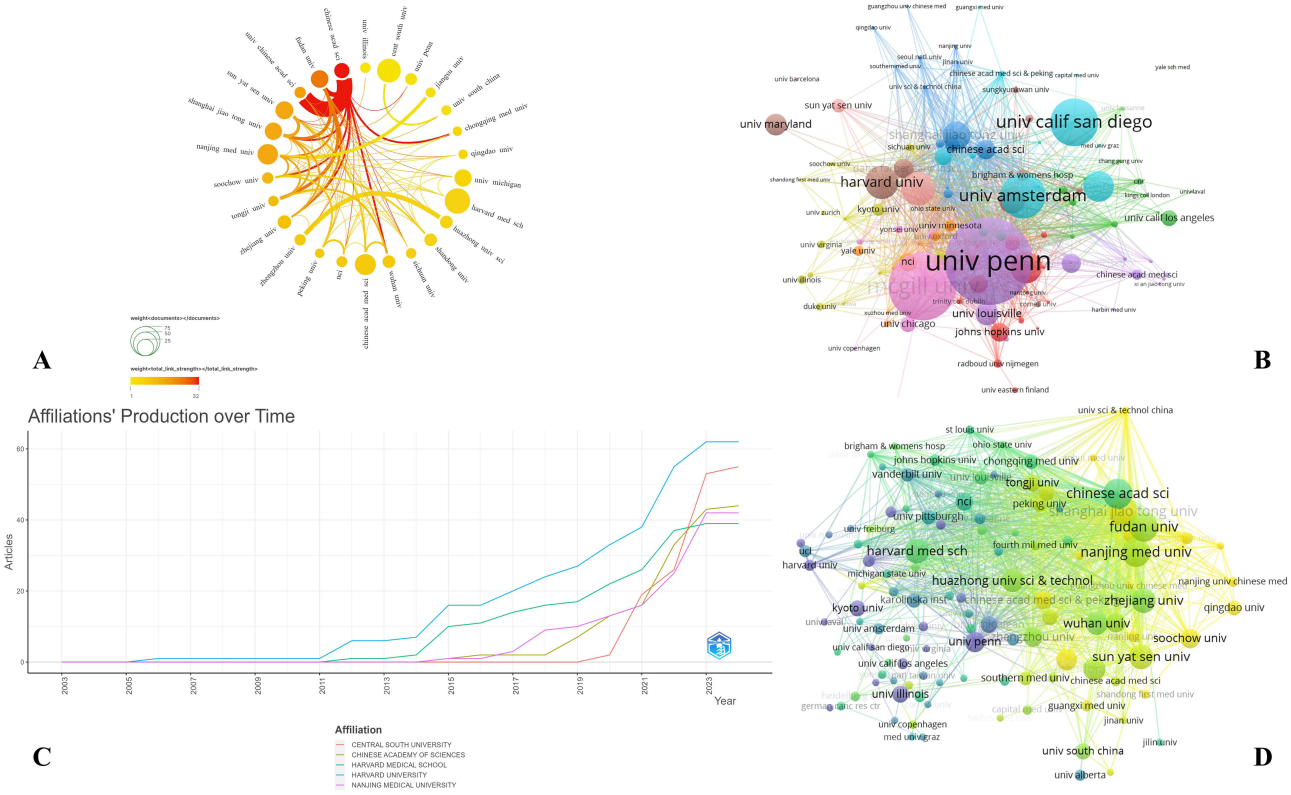

Figure 5 Chart of institutional cooperation and publication trends. (**A**)Visualization of university/institution collaboration network, (**B**) Co citation graph of universities/institutions, (**C**) Annual production trend of the top 5 universities/institutions with publication volume, (**D**) Coupling development trend graph of universities/institutions.

Table 2 The Top 10 Institutions with the Highest Number of Publications on Immune Metabolism in the Field of Cancer

Rank	Institutions	Countries/Regions	Count	H-index	Total Citations
1	Harvard University	USA	62	21	3140
2	Central South University	China	55	11	311
3	Chinese Academy of Sciences	China	44	16	1032
4	Nanjing Medical University	China	42	11	527
5	Harvard Medical School	USA	39	19	2951
6	University of Pennsylvania	USA	38	14	4360
7	Sun Yat-sen University	China	33	11	712
8	Fudan University	China	32	12	844
9	Shanghai Jiao Tong University	China	31	10	1411
10	University of Michigan	USA	31	10	888

Figure 7C. Single country publications (SCP) indicate that all authors of an article are from the same country, while multiple country publications (MCP) indicate that the authors come from different countries, signifying international collaboration. This suggests that China has the most collaborative authors in this field, but internal collaboration within China still accounts for a larger proportion, highlighting the need to strengthen international cooperation, as shown in Figure 7D. Table 4 lists the top 10 authors by publication volume and the top 10 authors by co-citation counts. These authors have significant academic influence in the field.

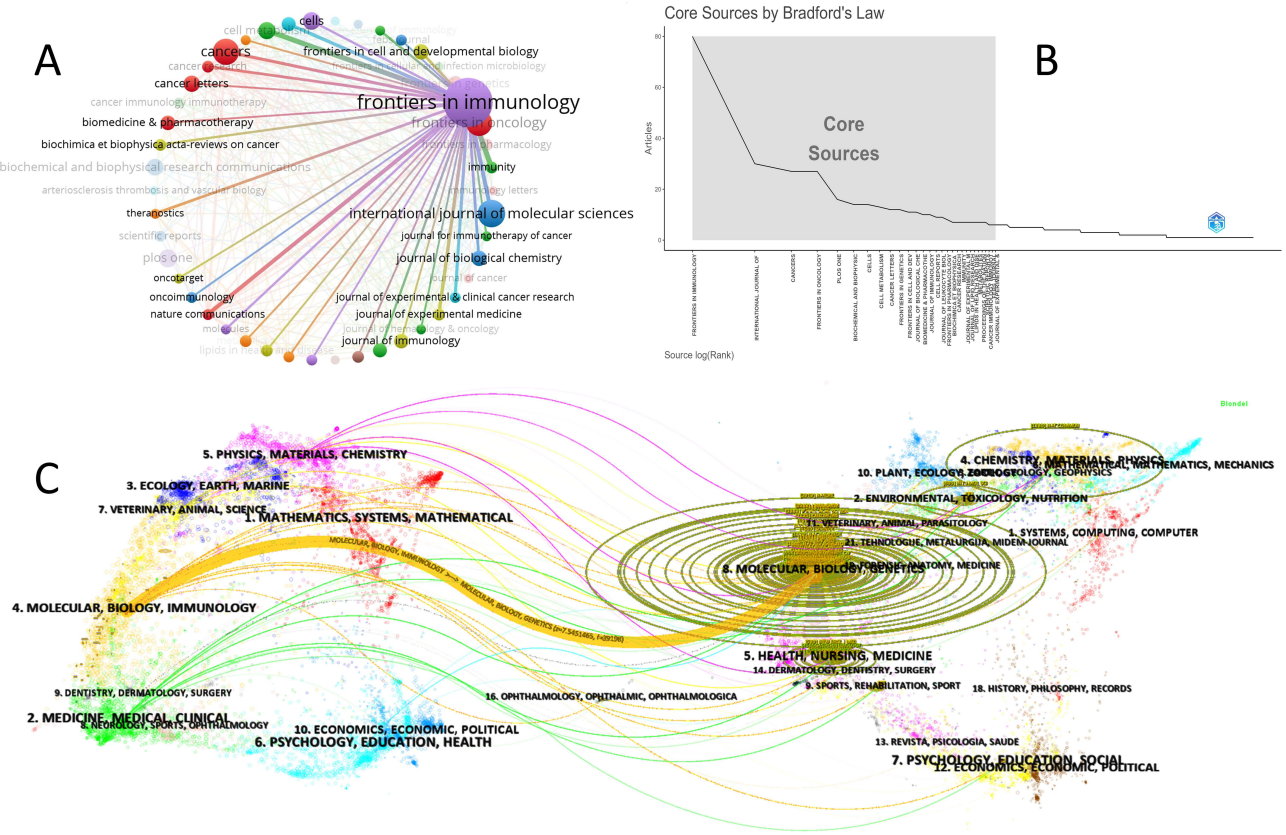

Figure 6 Visualization map of published journals. (**A**) Journal co-occurrence map, (**B**) core journal based on Bradford's law, (**C**) journal double graph overlay.

Table 3 The Top 10 Journals with the Highest Publication Volume on Immune Metabolism in the Field of Cancer

Rank	Journal title	Country	Count	IF (2022)	JCR (2022)	TLS	Total Citations	H-index
1	Frontiers in immunology	Switzerland	80	7.3	Q1	216	2237	22
2	International journal of molecular sciences	Switzerland	30	5.6	Q1	57	555	12
3	Cancers	Switzerland	27	5.2	Q2	70	279	10
4	Frontiers in oncology	Switzerland	27	4.7	Q2	115	238	9
5	PLoS one	United Kingdom	16	3.7	Q2	12	495	10
6	Biochemical and biophysical research communications	United Kingdom	14	3.1	Q2	14	338	11
7	Cells	Switzerland	14	6.0	Q2	41	213	7
8	Cell metabolism	United Kingdom	13	29.0	Q1	92	2984	13
9	Cancer letters	Netherlands	12	9.7	Q1	26	360	7
10	Frontiers in genetics	Switzerland	12	3.7	Q2	10	54	4

Co-Cited References

Co-cited literature forms an important knowledge base in a research field. In Figure 8A, co-cited literature forms four clusters. Analyzing these clusters is crucial for understanding the structure of the discipline, identifying research hotspots, promoting academic exchange and interdisciplinary collaboration, and supporting research management and

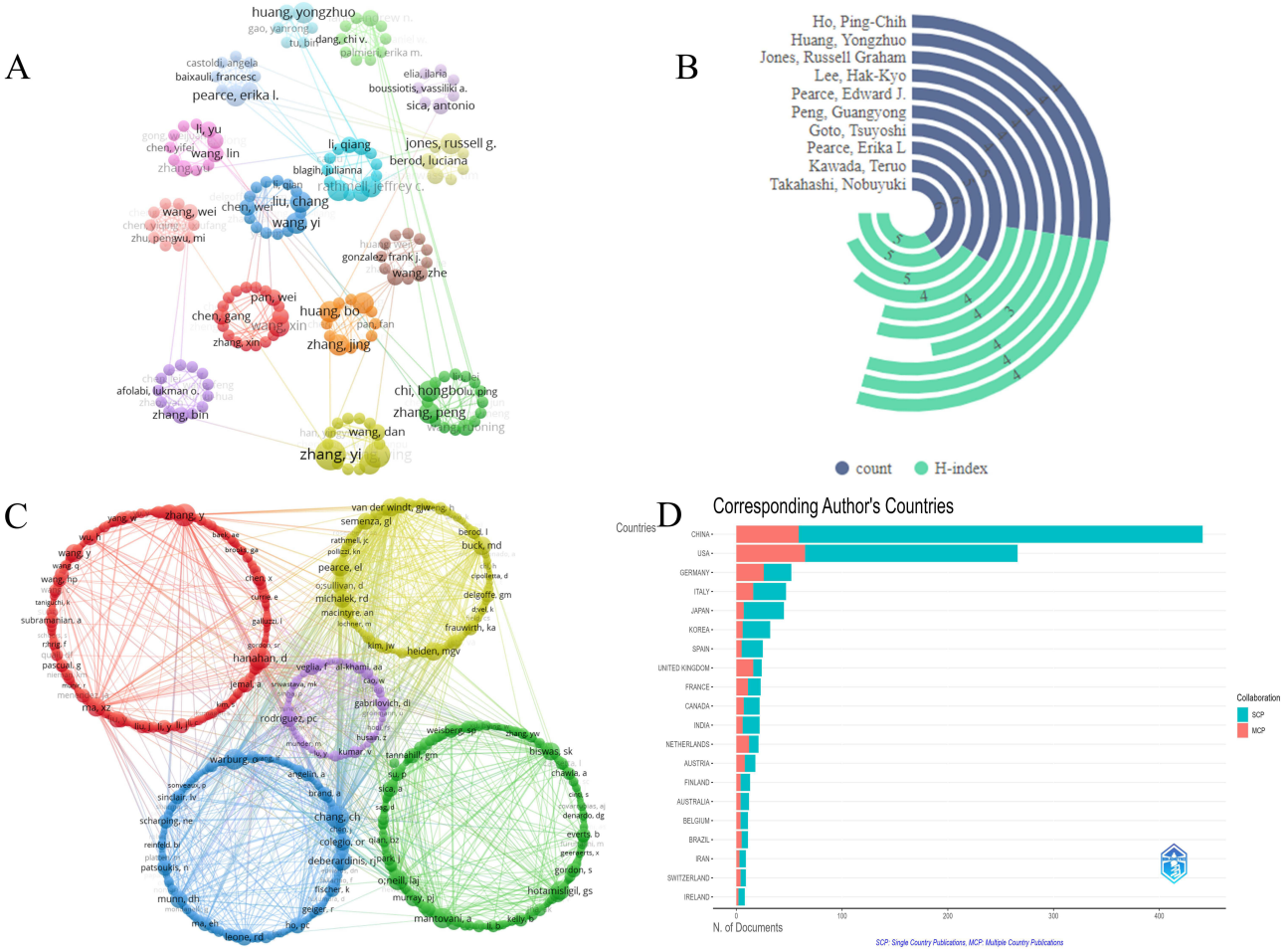

Figure 7 Author Collaboration Network Atlas of Immune Metabolism in the Field of Oncology. (**A**) Core author collaboration network, (**B**) Co cited author collaboration network, (**C**) Top 10 authors in terms of publication volume H-index jade block diagram, (**D**) Top 10 countries in terms of corresponding author count.

Table 4 Authors and Co Cited Authors of Immune Metabolism in the Field of Tumors (Top 10)

Rank	Author	Count	Total Citations	Co-Cited Author	Total Citations
1	Zhang, Yi	6	309	Chang, Ch	154
2	Huang, Lan	5	428	Zhang, Y	147
3	Kawada, Teruo	5	227	Hanahan, D	142
4	Liu, Yang	5	278	Warburg, O	123
5	Takahashi, Nobuyuki	5	227	Mantovani, A	118
6	Wang, Gang	5	34	O'neill, laj	115
7	Wang, Lei	5	141	DeberarDinis, Rj	112
8	Wang, Ying	5	113	Pearce, El	106
9	Goto, Tsuyoshi	4	160	Hotamisligil, Gs	102
10	Ho, Ping-Chih	4	116	Ma, XZ	99

policy-making. One of the key contributors, Douglas Hanahan, primarily focuses on identifying biomarkers for tumors. He considers the reprogramming of energy metabolism and the evasion of immune destruction as emerging hallmarks of cancer.[16] The team led by Stanley Ching-Cheng Huang[17] was the first to discover that macrophages mobilize fatty acids through the lysosomal pathway, promoting fatty acid oxidation (FAO) and the M2 polarization program. This discovery laid the foundation for understanding the interactions in immunometabolism. Matthew G. Vander Heiden's team[18] further elucidated the impact of aerobic glycolysis on tumor cell proliferation, emphasizing the relationship between metabolism and proliferation. The team led by Nikolaos Patsoukis[19] confirmed that PD-1 alters T cell metabolic reprogramming by inhibiting glycolysis while promoting lipolysis and fatty acid oxidation. The analysis of co-cited literature clusters thus

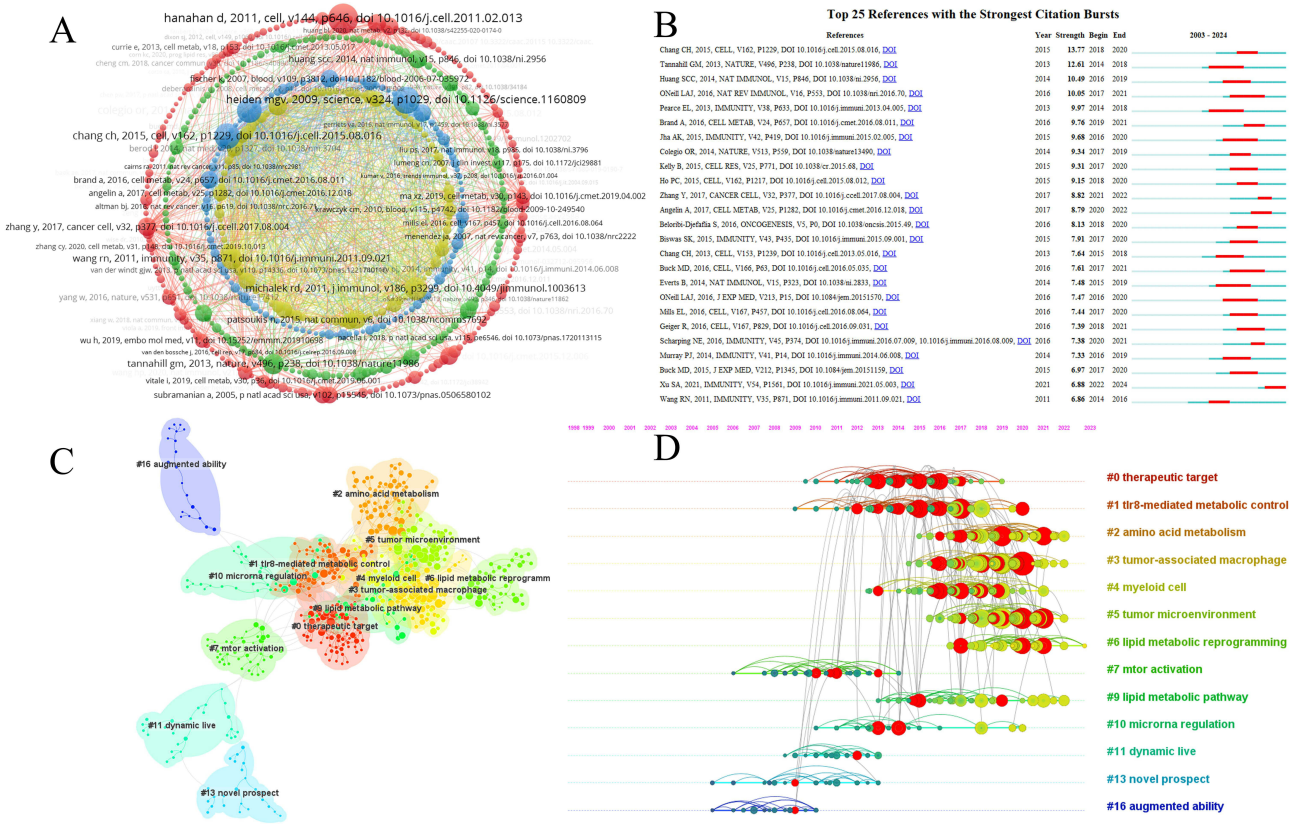

Figure 8 Visual mapping of cited literature. (**A**) thematic coupling analysis of research literature, (**B**) Top 25 References with the Strongest Citation Bursts, (**C**) clustering analysis of cited literature, (**D**) timeline analysis of cited literature.

provides significant insights into the fundamental research themes and developments in the field, guiding future research directions and fostering collaborative efforts.

Figure 8B presents the top 25 cited papers, with the study by G. M. Tannahill et al[20] exhibiting the highest burst strength (strength = 13.77), indicating that this paper marked a significant trend or turning point in the field during that period. Their research revealed that succinate, as a metabolite, plays a role in innate immune signaling, enhancing the production of interleukin-1β during inflammation and highlighting the role of metabolism in innate immunity. Furthermore, Erika L. Pearce et al[21] summarized the main pathways of immunometabolic interactions into two types: firstly, immune cells can regulate the metabolism of systemic immune organs; secondly, the metabolism of immune cells themselves affects immune efficacy. Their work emphasized that the functions of dendritic cells, T cells, B cells, and macrophages are regulated by metabolic pathways involving glucose metabolism, lipid metabolism, and amino acid metabolism. These highly cited papers underscore the importance of metabolic processes in immune responses and have contributed to a deeper understanding of immunometabolism, shaping subsequent research directions in this field.

In the co-cited literature clustering analysis, Figure 8C shows clusters labeled #0 "therapeutic target" and #1 "tlr8-mediated metabolic control", indicating that the discovery of therapeutic targets has been a central research focus in this field, including targets for regulating immunity and metabolism. Additionally, the timeline clustering in Figure 8D reveals that #2 "amino acid metabolism", #3 "tumor-associated macrophage", #4 "myeloid cell", #5 "tumor microenvironment", and #6 "lipid metabolic reprogramming" have been recent research hotspots. This suggests that glucose metabolism, lipid metabolism, amino acid metabolism, the tumor microenvironment, and immune cells are currently key focal points in the research of this field. These clusters highlight the evolving areas of interest and the emerging trends that are shaping the future directions of research in immunometabolism and oncology.

Keyword Analysis

The keyword bubble chart in Figure 9A indicates that topics such as "Lipid Metabolism in Cancer Cells", "Tumor Immune Responses", "Role in Tumor Progression", "Interaction between Immunity", "Levels in Macrophages", and "Protein Factors" are focal points of research in this field. Further exploration of research themes over time reveals three main development stages in this field over the past 20 years, as shown in Figure 10B. From 2003 to 2017, metabolism, tumor-associated macrophages, and inflammation were foundational research topics. Figure 9B shows that during this stage, "tumor necrosis factor" was a key regulatory factor with the highest burst strength (strength = 12.9), while "gene-expression" was the main form of research with significant influence (strength = 11.59). The focus during this period was on exploring the impact of immunometabolism on tumor gene expression, which plays a critical role in tumorigenesis.

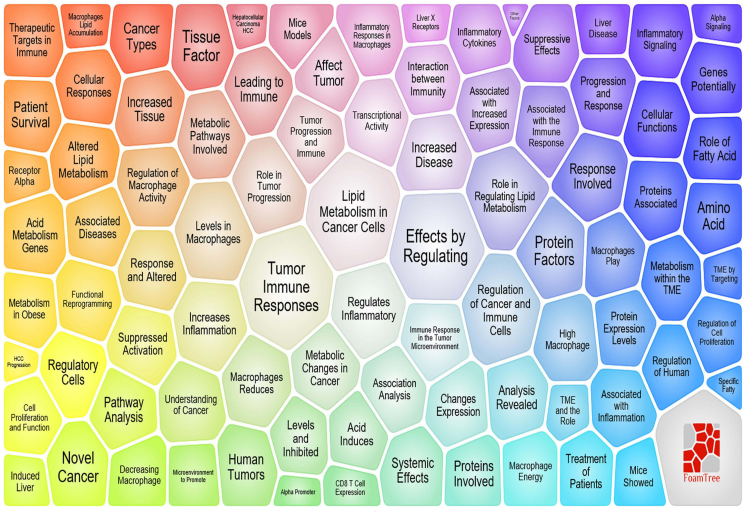

Figure 9 Keyword frequency analysis. (**A**) Bubble chart of keyword co-occurrence; (**B**)Top 25 Keywords with the Strongest Citation Bursts.

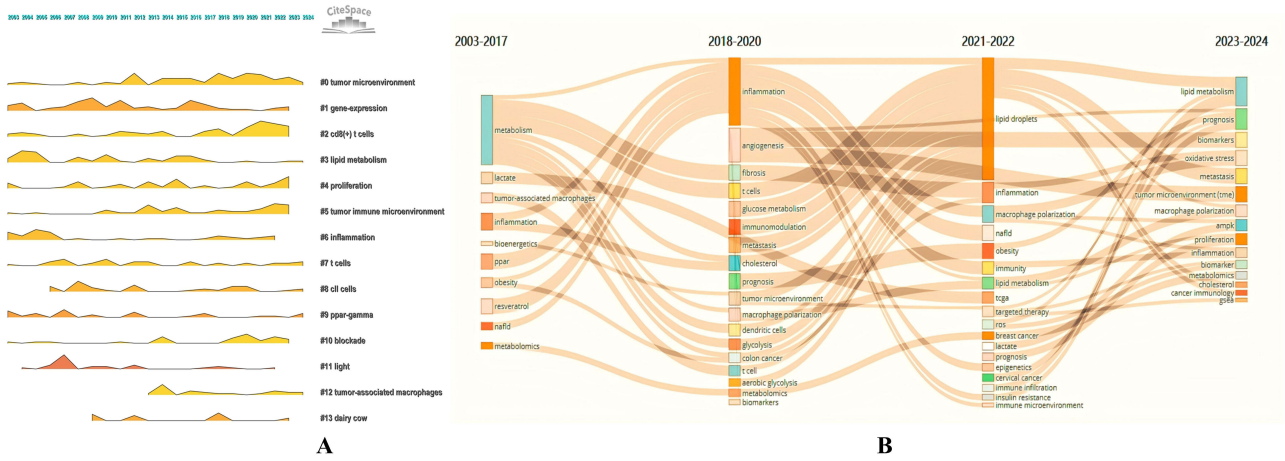

Figure 10 Keyword Timeline Analysis. (**A**) A mountain map of keyword clustering; (**B**) Thematic Evolution in the Keywords Plus from 2003 to 2023.

From 2018 to 2020, new research directions emerged, such as tumor angiogenesis, fibrin, glucose metabolism, and T cells. During this phase, topics like "glucose" (strength = 5.55) and "tumor microenvironment" (strength = 5) had significant influence. The emphasis was on studying the mechanisms by which metabolism and immunity affect tumor cell metastasis. From 2021 to 2022, there was increased attention on lipid metabolism, inflammation, oxidative stress, and therapeutic targets. Figure 9B indicates that "tumor associated macrophages" (strength = 4.67) and "regulatory t" (strength = 4.02) had high influence during this period. In 2023 to 2024, further developments occurred in lipid metabolism, prognosis, biomarkers, inflammation, and oxidative stress. Figure 10A shows that research areas such as "#0 tumor microenvironment", "#2 cd8(+) t cells", and "#5 tumor immune microenvironment" developed the fastest. The focus during this stage was on tumor prognosis, including recurrence and immune evasion mechanisms of tumor cells. In summary, immune cells and metabolism play crucial roles in the occurrence and development of tumor cells. The research trends indicate an evolving and deepening understanding of how metabolic pathways and immune responses intersect to influence tumor progression and treatment outcomes.

Discussion

Research Hotspots

T Cells

T cells are a crucial component of the adaptive immune system and play a vital role in antitumor immunity. The proliferation and activation of T cells require metabolic pathways to provide energy and intermediary metabolites, with the mTOR (mechanistic target of rapamycin) signaling pathway being key in this process.[22] Activation of mTORC1 promotes glycolysis and protein synthesis, thereby supporting cell proliferation and growth.[23] Glutamine metabolism provides carbon and nitrogen for the biosynthesis needs of T cells,[24] while lipid synthesis supplies raw materials for cell membrane formation. T cells exhibit different metabolic modes at different stages; resting T cells primarily rely on the tricarboxylic acid (TCA) cycle for energy, whereas glycolysis is the predominant metabolic pathway in rapidly proliferating and activated T cells.[25]

Furthermore, different subtypes of T cells utilize diverse metabolic pathways. mTORC1 is highly active in effector T cells, promoting glycolysis and protein synthesis.[26] Conversely, AMPK (adenosine monophosphate-activated protein kinase) is active in regulatory T cells, promoting fatty acid oxidation and inhibiting glycolysis to maintain energy balance.[27] Knocking out ASCT2 (glutamine transporter) and reducing mTORC1 activity can impede the production and function of Th1 and Th17 cells. During cellular stress, the activation of AMPK maintains cellular ATP balance and growth by inhibiting the mTOR signaling pathway.[28] The balance between mTOR and AMPK determines T cell proliferation and function.

In the tumor microenvironment (TME), nutrient competition and the accumulation of metabolic waste lead to the metabolic reprogramming of T cells. The hypoxic environment within the TME activates hypoxia-inducible factor-1α (HIF-1α), which significantly impacts T cell metabolism.[29,30] HIF-1α promotes glycolysis, but under severe hypoxia, the glycolytic products cannot be efficiently utilized, resulting in insufficient energy supply for T cells, which further hinders their immune function.[31,32] Therefore, metabolic pathways determine the proliferation, growth, and activation of T cells, playing a crucial role in the prognosis of tumors.

B Cells

Bone marrow-derived B cells play a crucial role in humoral immunity. Aerobic glycolysis is the primary energy source for B cell maturation and activation.[33] Lactate dehydrogenase (LDH) is a key enzyme in aerobic glycolysis, consisting of tetramers formed by LDHA or LDHB subunits.[34] Research has shown that knocking out LDHA reduces the frequency of B cell production, and serum levels of IgG1 and IgA decrease, while IgM concentration remains unchanged[35] These results indicate that LDHA deficiency impacts the role of B cells in humoral immunity. Understanding the metabolic requirements and pathways of B cells is essential for elucidating their function in immune responses and could inform therapeutic strategies for enhancing humoral immunity.

Sphingosine-1-phosphate (S1P) is an important lipid signaling molecule that participates in the transport of immune cells through its interaction with the S1P1 receptor.[36] During B cell development, the S1P/S1P1 signaling pathway plays a crucial role in the migration and release of immature B cells.[37] Specifically, the S1P1 receptor is expressed on the surface of immature B cells and, upon binding with S1P, activates downstream signaling pathways that regulate gene expression and cytoskeletal reorganization related to cell migration. This signaling mechanism promotes the migration of immature B cells from the bone marrow into the bloodstream, allowing these B cells to further migrate to secondary lymphoid organs such as the spleen and lymph nodes, where they mature and participate in immune responses.[38] In summary, glycolysis and lipid metabolism are not only sources of energy for B cell proliferation and activation but also play critical roles in regulating their immune functions. Understanding these metabolic pathways is essential for developing strategies to enhance B cell-mediated immunity.

Macrophage

In recent years, macrophages have garnered significant attention in antitumor research. In the tumor microenvironment, macrophages play a double-edged sword role.[39,40] M1 macrophages exhibit antitumor activity by producing pro-inflammatory cytokines (such as IL-1, IL-12, IFN-γ, and TNF-α) and reactive oxygen species (ROS), directly killing tumor cells and enhancing the antitumor activity of T cells.[41–43] However, M2 macrophages promote cancer cell proliferation and migration by secreting IL-10 and TGF-β. Additionally, M2 macrophages secrete VEGF, promoting angiogenesis and tumor growth.[44] Therefore, regulating the polarization state of macrophages is crucial for enhancing antitumor immune responses and mitigating tumor cell immune evasion.[45] M1 macrophage polarization can be enhanced by IFN-γ and LPS, while M2 polarization is promoted by IL-4, IL-10, and IL-13.[46] Thus, promoting the polarization of M2 macrophages to M1 macrophages to activate antitumor immune responses is an ideal strategy.[47] This strategy holds broad clinical application prospects in immunotherapy and personalized treatment.

M1 macrophages primarily rely on aerobic glycolysis to generate energy, favoring the glycolytic pathway even under aerobic conditions. This metabolic preference, which includes impaired oxidative phosphorylation (OXPHOS), supports their rapid activation of immune responses.[48] Conversely, M2 macrophages generate ATP mainly through the TCA cycle coupled with OXPHOS and rely on fatty acid oxidation for energy.[49] Therefore, metabolic reprogramming of macrophages is crucial for the expression of their biological activity. The metabolic reprogramming of macrophages not only determines their energy supply and physiological state but also directly influences their functions and roles in different immune environments. Understanding these metabolic pathways is essential for developing strategies to modulate macrophage function in cancer therapy and other immune-related conditions.

Natural Killer Cells

Natural killer (NK) cells can directly recognize and kill tumor cells without the need for antigen presentation. Therefore, enhancing the activity or quantity of NK cells is a critical focus of current antitumor immunotherapy. Glucose is the

primary energy source supporting NK cell oxidative phosphorylation metabolism, playing a significant role in promoting NK cell development and activation. However, excessive mitochondrial uptake of fatty acids in NK cells can lead to dysfunction, and mitochondrial dysfunction is a key feature of weakened NK cell antitumor responses.[50] Additionally, IL-15 produced by dendritic cells can induce the activation of the central metabolic regulator mTOR, further controlling the metabolic reprogramming of NK cells to exert antitumor effects. However, sustained IL-15 stimulation can reduce NK cell glucose oxidative phosphorylation activity, thereby diminishing their antitumor capabilities.[51] To optimize NK cell function in antitumor therapy, researchers are exploring ways to balance their metabolic needs and functional maintenance. Ensuring adequate glucose supply to NK cells in the tumor microenvironment, by inhibiting CD36 activity to block lipid uptake, could be an effective method to maintain NK cell effector functions in lipid-rich environments.[52] Additionally, optimizing IL-15 administration (such as intermittent or low-dose IL-15 stimulation) can effectively enhance NK cell activity and cytotoxicity.[53] This metabolism-based strategy not only helps improve NK cell killing efficiency but also overcomes the inhibitory effects of the tumor microenvironment on NK cell function, thereby significantly enhancing the effectiveness of antitumor immunotherapy.

Research Trends

The Interaction Between Tricarboxylic Acid Cycle and Immunity

The tricarboxylic acid (TCA) cycle plays a critical regulatory role in the functioning of the immune system. It significantly influences immune cell functions and effects through pathways such as energy supply, signal regulation, cell polarization, and redox balance.[54,55] As a crucial intracellular metabolic pathway, the TCA cycle generates a substantial amount of ATP via oxidative phosphorylation, providing energy for immune cells to support their proliferation, migration, and immune effector functions. Metabolic intermediates of the TCA cycle, such as succinate, citrate, and α-ketoglutarate, are not only important energy molecules but also serve as signaling regulators that impact immune responses. For instance, succinate can activate the NLRP3 inflammasome by enhancing HIF-1α production, thereby promoting inflammatory responses.[56] Citrate can regulate gut microbiota to enhance immunity.[57] α-Ketoglutarate -mediated epigenetic modifications can regulate the expression of programmed cell death protein 1 (PD-1) and its ligand PD-L1 in cancer cells.[58]

The TCA cycle plays a decisive role in the polarization of macrophages and T cells. M1 macrophages rely on glycolysis and partial TCA cycle metabolism to produce reactive oxygen species (ROS) and succinate, enhancing their pro-inflammatory and antimicrobial functions. [59,60] In contrast, M2 macrophages depend on a complete TCA cycle and fatty acid oxidation to generate ATP and NADPH, supporting anti-inflammatory responses and tissue repair.[61] Effector T cells primarily rely on glycolysis and partial TCA cycle metabolism to rapidly generate energy to meet the demands of immune responses.[62] In contrast, memory T cells depend on fatty acid oxidation and the TCA cycle to generate long-term energy reserves, maintaining sustained immune surveillance.[63]

The activity of the TCA cycle is closely linked to the cellular redox state, influencing the generation and clearance of reactive oxygen species (ROS). While a moderate amount of ROS is crucial for pathogen defense, excessive ROS can lead to cellular damage and tissue inflammation.[64] Additionally, TCA cycle metabolites can impact metabolism and epigenetics, thereby regulating immune functions.[65] Research in immunometabolism has revealed the potential of metabolic targets in modulating antitumor immunity, with combined immunotherapy and metabolic therapy showing promising prospects.[66] Therefore, in-depth research on the interactions between the TCA cycle and the immune system is crucial for developing novel immunotherapeutic strategies to enhance antitumor immune responses. The regulatory effects of TCA cycle intermediates on immune cells are summarized in Table 5.

Pending Challenges and Clinical Concerns

In tumor immunometabolism research and clinical applications, the complexity of metabolic pathways, identification of metabolic markers, metabolic reprogramming of immune cells, and metabolic competition between tumor and immune cells pose major challenges.

Firstly, the metabolic pathways in the tumor microenvironment are intricate, involving interactions among multiple biochemical pathways. Tumor cells preferentially undergo aerobic glycolysis via the Warburg effect to rapidly generate

Table 5 Regulatory Effects of TCA Cycle Intermediates on Immune Cells

Name	T cell	B cell	NK cell	Dendritic Cell	Macrophage
Citric acid	Reduce the number of regulatory T cells Th1 and Th17.[67]	Promote B cell differentiation to produce IgA and IgG.[68]	Regulating immune stimulating NKG2D ligand mica in cancer cells.[69]	Inducing dendritic cell maturation and promoting T cell infiltration within tumors.[70]	Strong inhibition of M1 phenotype macrophages and weak inhibition of M2 phenotype macrophages can effectively reduce the M1/M2 macrophage ratio.[71]
Isocitric acid	Mitochondrial isocitrate dehydrogenase 2 gene deletion promotes differentiation of memory CD8+T cells.[72]	0	0	0	0
α-ketoglutaric acid	Promote the proliferation and activation of CD8 +T cells.[73]	Increase H3K27 trimethylation of B cells, promote the expression of AtM B cell related transcription factors Tbet and BATF, and induce differentiation of AtM B cells.[74]	0	**0**	Promoting M2 macrophage activation.[75]
Succinyl coenzyme A	0	0	0	0	The valine succinyl CoA axis inhibits the production of IL-1 β by M1 macrophages in the process mediated by phenylalanine (Phe).[76]
Succinic acid	0	Promoting B cell activation through the succinate receptor 1-interferon regulatory factor 5-B cell activation factor signaling pathway.[77]	Improving NK cell activity and enhancing anti-tumor effect on meat cancer.[78]	Stimulating dendritic cells through its receptor succinate receptor 1.[79]	Promoting chemotaxis and polarization of M1 macrophages.[80]
Fumaric acid	Blocking the activation of CD8 +T cells and inhibiting T cell anti-tumor immune function.[81]	Inhibition of B cell activation and function by directly inactivating tyrosine protein kinase LYN.[33]	Inhibition of CD56+NK cell count.[82]	Inhibiting DC maturation by reducing the expression of co stimulatory molecules and MHC class II, as well as blocking cytokine secretion.[83]	Yanhusuo acid ester promotes NRF2 expression and anti-inflammatory effects, and activates macrophages in vivo.[84]
Malic acid	Sustainable ammonia neutral glutamine catabolism in CD8 +T cells.[85]	0	Increase the number and function of NK cells.[86]	0	Inducing polarization of M2 macrophages and restoring interleukin-10 levels in a SOCS2 dependent manner.[87]
Oxaloacetic acid	Supplementing oxaloacetic acid, malic acid, and fumaric acid can restore T cell function.[88]	0	0	0	0

Note: 0 represents that no relevant research has been reported yet.

energy and biosynthetic precursors. Simultaneously, lipid metabolism and amino acid metabolism play crucial roles in the growth and survival of tumor cells.[89] These metabolic changes not only promote tumor cell proliferation but also affect the function of immune cells. Research has shown that fatty acids drive the proliferation and migration of breast cancer cells and promote tumor growth and immune evasion through a cyclooxygenase-dependent pathway.[90]

Secondly, identifying biomarkers related to tumor immunometabolism is crucial for personalized treatment. These biomarkers can help predict patient responses to therapy and monitor disease progression. However, finding highly specific and sensitive biomarkers in different tumor microenvironments presents significant challenges. Plasma lactate levels can serve as a potential marker for evaluating the state of the tumor immune microenvironment, with higher lactate concentrations being associated with poorer prognosis. Targeting glutamine metabolism can enhance tumor-specific immunity and reduce the accumulation of lactate and immunosuppressive cells in the tumor microenvironment[91] herefore, lactate may be an ideal biomarker in acidic microenvironments.

Additionally, studies have shown that metabolic reprogramming in the tumor microenvironment contributes to the formation of an immunosuppressive microenvironment, inhibiting the antitumor capabilities of immune cells.[92] This metabolic reprogramming prevents immune cells from effectively killing tumor cells, affecting the efficacy of immunotherapy. Lastly, tumor cells and immune cells compete for limited nutritional resources in the microenvironment, leading to intense metabolic competition. Tumor cells efficiently utilize metabolites such as glucose and glutamine, thereby weakening the energy supply and functional activity of immune cells, resulting in tumor immune evasion.[93] Therefore, research aimed at enhancing the competitiveness of immune cells in the tumor microenvironment warrants further exploration.

Limitations

(1) Data Source and Coverage:This study only utilized the Web of Science Core Collection, PubMed, and Scopus databases, potentially missing relevant literature from other sources. Additionally, the inclusion criteria were limited to publications in English, which might overlook significant research published in other languages.

(2) Limitations of Bibliometric Analysis:While bibliometric analysis can reveal research hotspots and trends, it cannot assess the quality and innovation of individual studies. Metrics such as citation count and impact factor may be influenced by self-citation and journal policies, potentially affecting the accuracy of the analysis.

(3) Complexity of Interdisciplinary Research:Immunometabolism is a highly interdisciplinary field involving immunology, metabolism, oncology, and other disciplines. Differences in terminology and research methods across these fields can pose challenges in understanding and integrating the data, potentially impacting the comprehensive and accurate identification of research hotspots and trends.

Conclusions and Prospectives

Over the past 20 years, significant progress has been made in the field of immunometabolism in cancer, with a total of 3320 related papers published. These studies span 71 countries/regions, involving 1738 institutions and 8090 authors, published in 509 journals. Current research hotspots focus on T cells, B cells, macrophages, and NK cells. Additionally, the main challenges and promising future directions include the interactions between the TCA cycle and immunity, the complexity of metabolic pathways, identification of metabolic biomarkers, metabolic reprogramming of immune cells, and metabolic competition between tumor cells and immune cells. Addressing these challenges requires further research to advance the field and provide new therapeutic strategies for clinical applications.

The essence of cancer development lies in the activation of oncogenes and the mutation of tumor suppressor genes. While treating tumors from the perspective of immunometabolism cannot alter genetic mutations, immunometabolic therapy can improve the microenvironment, enhance immune cell functions, and increase the body's ability to monitor genetic mutations, thereby preventing further carcinogenesis of other cells. This approach keeps cancer cell genetic mutations within the controllable range of the body, reducing the risk of tumor recurrence and metastasis and improving overall treatment outcomes.

With deeper research into cancer and immunometabolism, there is potential to reconceptualize cancer as a chronic disease similar to hypertension or diabetes. The goal would be to slow disease progression and improve patient quality of

life rather than attempting to eradicate all mutant genes or cancer cells. This paradigm shift focuses on disease management and control, aiming to maintain the balance within the body and extend the survival and well-being of patients.

Data Sharing Statement

All datasets presented in this study can be found in the WoSCC,PubMed, and Scopus database.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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