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Global Research Trends of Tumor Microenvironment and Epigenetics

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Global Research Trends of Tumor Microenvironment and Epigenetics

Abstract: The tumor microenvironment (TME) critically influences tumor progression, therapeutic response, and clinical outcomes. Epigenetic mechanisms can re-program the TME from an anti-tumor to an immunosuppressive state by modulating the phenotypic plasticity of both immune and tumor-associated stromal cells. Consequently, a comprehensive understanding of epigenetic regulators in the TME is essential for optimizing cancer-therapy strategies. We employed the bibliometric platforms CiteSpace and VOSviewer to perform citation-coupling and co-occurrence analyses of 5,492 publications indexed in the Web of Science Core Collection that pertain to the intersection of the tumor microenvironment and epigenetics (TMEE). Analyses were stratified by country, institution, author, keyword, journal, and reference. China leads global output with 2,825 publications (51.44%), whereas the United States exhibits the highest betweenness centrality (0.36), underscoring its influential role in collaborative networks. Zhejiang University demonstrates the longest citation half-life (12.5 years), reflecting sustained scientific impact. Liu Jinhui and Eyad Elkord are the most prolific authors, each contributing 12 TMEE-related articles. Among epigenetic modifications, DNA methylation is the earliest and most extensively studied mechanism, whereas N6-methyladenosine (m^6A) has emerged as the most intensively investigated modification in recent years. Tumor immunity now represents a central and rapidly evolving frontier in TMEE research. This bibliometric study provides a panoramic and data-driven overview of global TMEE research, offering scholars a concise roadmap for identifying current hotspots and future directions.

Key Words: Tumor microenvironment; Epigenetics; bibliometrics；DNA methylation；

Tumor immunity

1. **Introduction**

The tumor microenvironment (TME) creates conditions that favor the proliferation and dissemination of malignant cells. It is composed of diverse cell types-including inflammatory cells, fibroblasts, neurons, and vascular endothelial cells-which collectively accelerate tumor progression by secreting bioactive molecules. These

factors either directly activate oncogenic signaling pathways within cancer cells or remodel the surrounding milieu [1]. Beyond driving tumor growth, the TME profoundly influences therapeutic efficacy and clinical outcomes. Soluble factors released by either tumor or stromal cells can induce microenvironment-mediated drug resistance, while physical interactions-such as adhesion of tumor cells to stromal fibroblasts or the extracellular matrix-can further attenuate treatment responses [2]. Recent investigations have demonstrated that epigenetic dysregulation can reprogram both immune and tumor-associated stromal cells (e.g., fibroblasts and endothelial cells), thereby reshaping the TME from an anti-tumor to an immunosuppressive state [3]. Consequently, pharmacologic targeting of epigenetic regulators represents a promising strategy for TME reprogramming and improved cancer therapy.

Epigenetics constitutes a critical interface between environmental exposures and disease phenotypes. The principal epigenetic mechanisms now recognized include chromatin remodeling, genomic imprinting, DNA methylation, histone post-translational modifications, non-coding RNA networks, and RNA chemical modifications. Collectively, these layers of regulation modulate biological phenotypes by intervening at multiple stages of RNA metabolism—transcription, nuclear export, processing, stability, degradation, and translation. Extensive evidence demonstrates that these epigenetic alterations drive tumorigenesis and progression by orchestrating the functional reprogramming of the TME [4].

Bibliometrics is a quantitative research discipline that employs statistical methods to examine the distribution, inter-relationships, temporal dynamics, and managerial aspects of the scientific literature. By doing so, it elucidates the underlying structure, intrinsic characteristics, and developmental trajectories of scholarly publications [5]. In medicine, bibliometric analyses can rapidly map macro-level publication patterns across massive datasets, offering investigators a panoramic view of global research activity and highlighting potential collaborators. At the micro level, these techniques trace the evolution of research hotspots, thereby providing an evidence-based foundation for anticipating future directions.

After refining our search strategy, we retrieved 5,492 TMEE-related publications from the Web of Science Core Collection. Leveraging advanced visualization tools—CiteSpace and VOSviewer—we conducted a multidimensional bibliometric analysis covering publication trends, geographic distribution, source journals, citation networks, keyword co-occurrence, institutional affiliations, and author productivity. This study

equips researchers with a concise, data-driven overview of the latest advances in TMEE research and offers a novel framework for dissecting how epigenetic mechanisms remodel the TME to drive malignant progression.

2. Methods and Materials

2.1 Data sources and retrieval strategies

Data were extracted from the Web of Science Core Collection, chosen for its comprehensive scope, rigorous indexing standards, and seamless compatibility with leading bibliometric tools. To capture all publications highly pertinent to our topic, we used "tumor microenvironment" and "epigenetics" as primary search concepts and systematically expanded these with synonyms, hyponyms, and established abbreviations. The search was executed on 14 June 2025 at 20:00 UTC, and the resulting records were filtered according to predefined inclusion criteria, yielding a final dataset of 5,492 articles. The complete search strategy and workflow are illustrated in Figure 1.

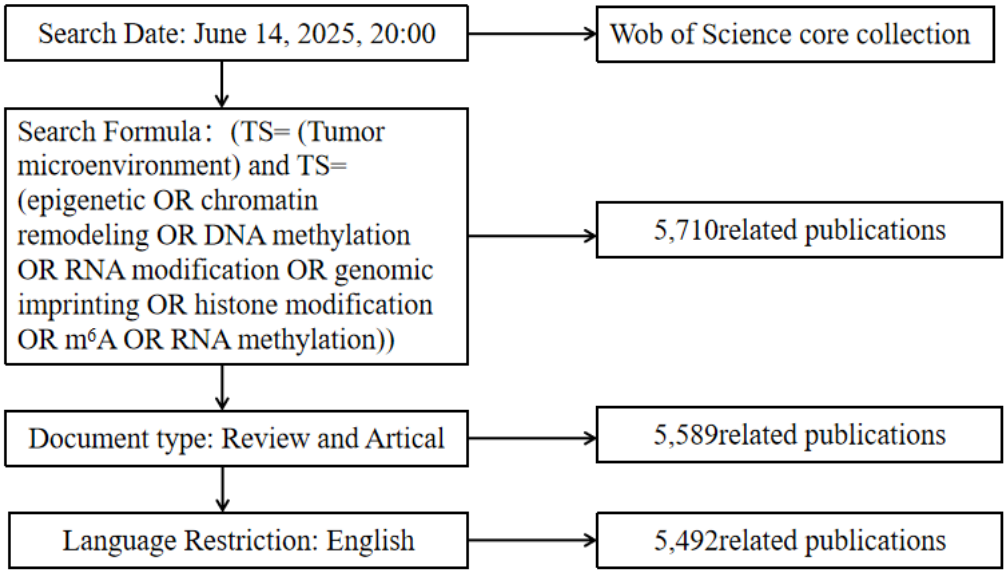


Figure 1. Literature retrieval strategies and steps

2.2 Data processing and analysis

We exported the retrieved records in "full record and cited references" format as TXT files. After weighting and data-model transformation in CiteSpace 6.3.1 (https://Citespace.podia.com), we obtained 5,492 unique documents: 3,496 original

articles and 1,996 reviews. The cleaned dataset was imported into CiteSpace for burst-word detection, timeline cluster analysis, and journal dual-map overlays. For multidimensional co-occurrence analysis, the same dataset was loaded into VOSviewer 1.6.20 (https://www.vosviewer.com) to generate clusters of countries, institutions, authors, and keywords. Annual output curves and international collaboration maps were dynamically rendered with the online bibliometric platform (https://bibliometric.com). Geographic cluster maps were produced with Scimago Graphica 1.0.50 (https://graphica.app/), and Pajek 5.19 (http://mrvar.fdv.uni-lj.si/paje) was used to refine keyword-cluster visualizations generated by VOSviewer.

3. Result

3.1 Analysis of the time trend of publication volume

To delineate temporal trends in TMEE research, we analyzed the publication years of the 5,492 retrieved articles after excluding incomplete 2025 data (Figure 2). The earliest TMEE study appeared in 1999, marking the inception of the field. Since then, publication output has evolved through three distinct phases: (1) 1999-2019: Incubation phase. Annual output grew slowly, reflecting early-stage exploration. (2) 2019-2022: Surge phase. Publications rose sharply, peaking in 2022 (n = 940), as the scientific community increasingly recognized the impact of epigenetic mechanisms on the TME. (3) 2022-2024: Consolidation phase. Annual output has stabilized above 870 papers, indicating that foundational insights have been achieved and the field has entered a mature, yet dynamic, state. Conducting a bibliometric analysis at this juncture enables researchers to rapidly grasp the current landscape and anticipate emerging research directions within TMEE.

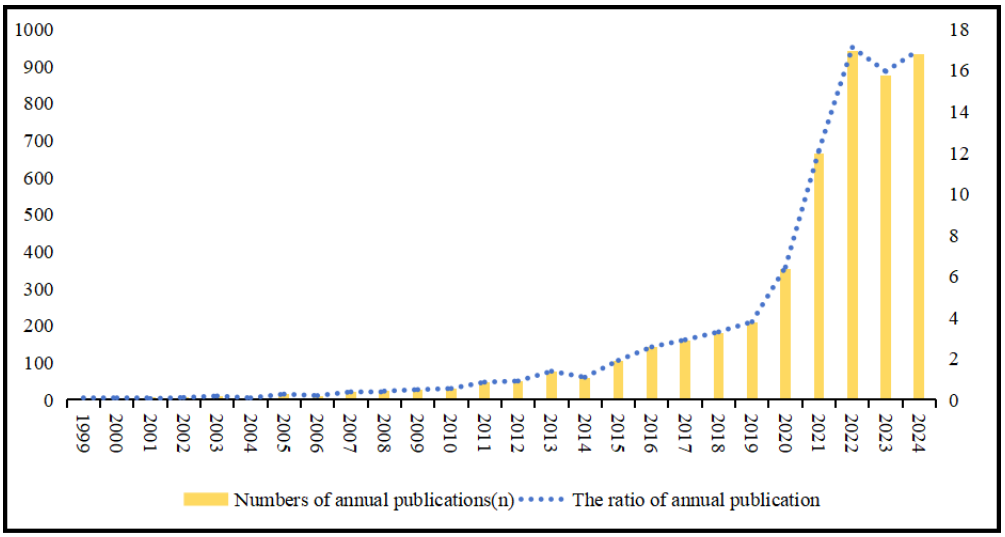


Figure 2. Analysis of the number of annual literature publications in TMEE

3.2 Country

The 5,492 records originate from 97 countries. Table 1 lists the 20 most prolific nations together with their network centrality values. China leads with 2,825 articles (51.44%), followed by the United States with 1,346 (24.51%); China's output thus exceeds half of the global total, underscoring its dominant role in TMEE research. Italy (n=312, 5.68%) and Germany (n=236, 4.30%) rank third and fourth, respectively, yet their combined output remains markedly lower than that of the top two countries. In terms of collaborative-network centrality, the United States scores the highest (0.36), affirming its pivotal position in international partnerships. Figure 3b further illustrates that, after the United States, the countries with comparatively high centrality are Italy (0.14), Saudi Arabia (0.12), France (0.12), and China (0.11).

To capture the longitudinal publication dynamics of each country, we plotted annual output curves (Figure 3a). Spain, Germany, and the United States initiated TMEE-related research in 1999 and dominated the early phase. China entered the field in 2010; despite its later start, it exhibited the steepest growth trajectory. Since 2021, China has annually contributed more than half of the world's publications, underscoring its pivotal role in driving the rapid expansion of TMEE research.

Figure 3c depicts the global co-authorship network. The United States displays the densest collaborative links, with China serving as its most frequent partner. National clustering (Figure 3d) reveals six distinct collaborative communities. The largest (blue) cluster centres on China, the United States, Canada and Australia, followed by the

brown cluster comprising Russia, France, Kazakhstan and Mexico.

Table 1. The top 20 countries and centers in terms of the number of literature publications.

Rank	Country	Record Count	% of 4,655	Centrality
1	CHINA	2825	51.438	0.11
2	USA	1346	24.508	0.36
3	ITALY	312	5.681	0.14
4	GERMANY	236	4.297	0.07
5	INDIA	186	3.387	0.06
6	ENGLAND	185	3.369	0.06
7	JAPAN	182	3.314	0.03
8	CANADA	145	2.64	0.03
9	FRANCE	143	2.604	0.12
10	SPAIN	134	2.44	0.05
11	AUSTRALIA	100	1.821	0.05
12	SOUTH KOREA	85	1.548	0.01
13	NETHERLANDS	74	1.347	0.01
14	SWITZERLAND	67	1.22	0.01
15	SAUDI ARABIA	62	1.129	0.12
16	BELGIUM	58	1.056	0.01
17	IRAN	56	1.02	0.03
18	POLAND	54	0.983	0.01
19	SINGAPORE	54	0.983	0.01
20	SWEDEN	52	0.947	0.01

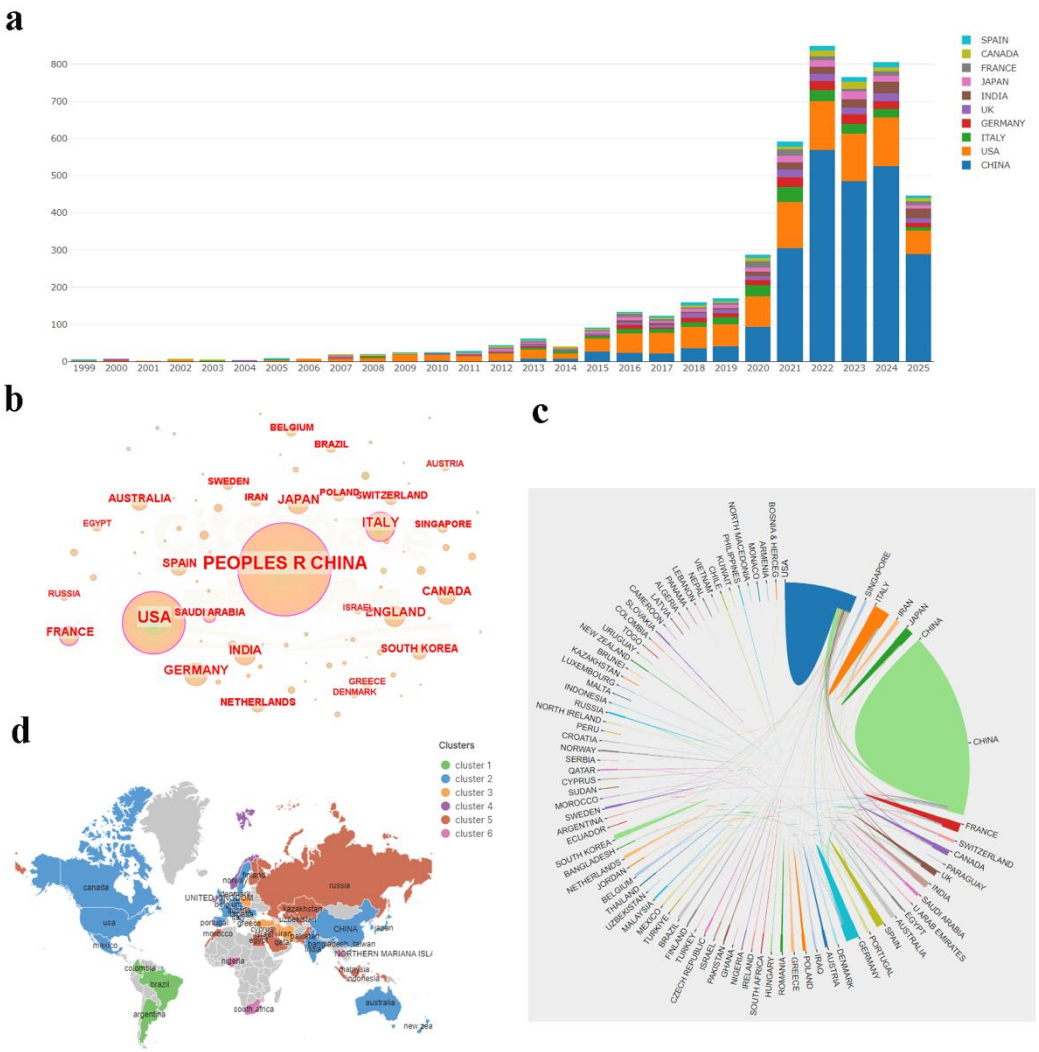


Figure 3. Visual Analysis of Countries.

(a) Annual publication share by country; (b) national centrality network; (c) international collaboration network; (d) country collaboration clusters. Note: (a) Generated with the online bibliometric platform; bar colors denote countries and bar heights indicate publication counts. (b) Produced with CiteSpace; node size reflects publication volume and the thickness of the purple outer ring denotes centrality. (c) Generated with the online bibliometric platform; node colors represent countries and connecting lines depict collaboration links. (d) Created with Scimago Graphica; node colors indicate cluster membership.

3.3 Institution

A total of 4,628 institutions have contributed to TMEE. Table 2 lists the 20 most productive. The top three—Shanghai Jiao Tong University (n=155), Central South University (n=147), and Sun Yat-sen University (n=144)—are all based in China.

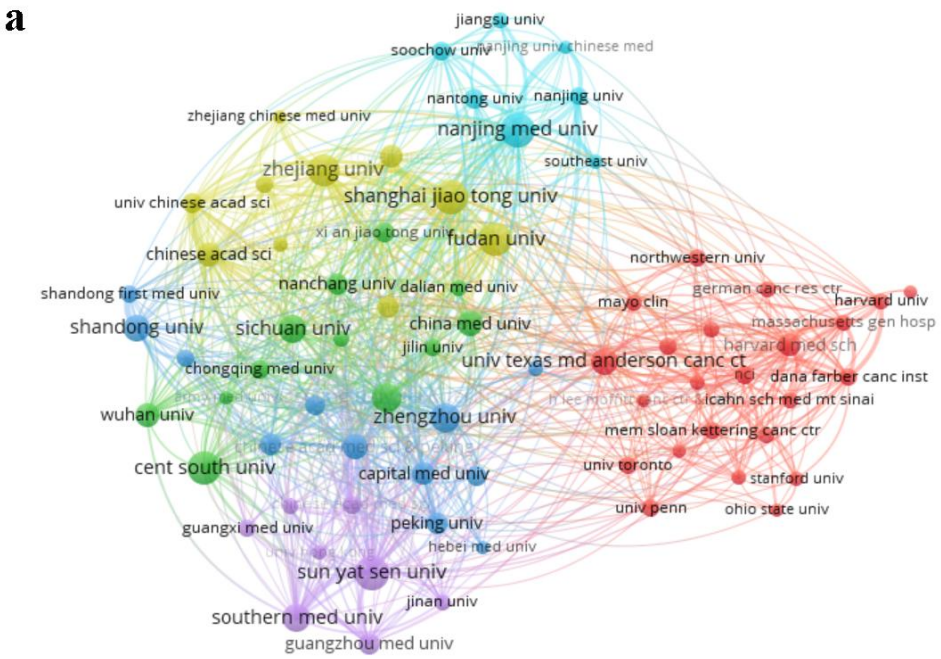
Among the top 20, 18 institutions are Chinese and 2 are American, reaffirming China and the United States as the field's dominant forces. Academic persistence was estimated by half-life: the longer the half-life, the more enduring the institution's impact. Within the top 20, Zhejiang University has the longest half-life (12.5 years), followed by the University of Texas MD Anderson Cancer Center (8.5) and Shanghai Jiao Tong University (7.5).

To examine inter-institutional collaboration, we applied a 25-publication threshold and retained 72 institutions for network mapping (Figure 4a). The analysis revealed six distinct clusters: (1) The largest (red) cluster—anchored by Case Western Reserve University, Dana-Farber Cancer Institute, and the German Cancer Research Center—comprises members from multiple countries, yet contains no Chinese institutions. (2) The second-largest (green) cluster is led by Army Medical University, Central South University, and China Medical University. The remaining four clusters are dominated almost exclusively by Chinese universities or research institutes. This pattern indicates robust domestic collaboration among Chinese institutions but comparatively limited cross-border engagement. Although China exhibits high national-level centrality, this is driven primarily by its sheer publication volume; institutional-level international linkages remain an area for strategic strengthening.

To evaluate the temporal impact of individual institutions, we quantified their "burst intensity" across the study period (Figure 4b). Three archetypes emerged: (1) Early-persistent contributors: Ohio State University, Johns Hopkins University, and the University of Pennsylvania have remained continuously active since the inception of the field, sustaining their influence to the present. (2) Recent-surge contributors: New York University, the Icahn School of Medicine at Mount Sinai, and IRCCS have experienced sharp bursts in output over the past few years, aligning their research with current hot topics. (3) Prolific-burst contributors: Harvard Medical School not only ranks among the top 20 high-yield institutions but also exhibited a pronounced surge from 2016 to 2020, reflecting a major scientific breakthrough during that window. Notably, among institutions that displayed clear burst dynamics, only one is Chinese, whereas 18 of the top 20 high-yield institutions are Chinese. This divergence indicates that, despite China's substantial overall output, its institutions have yet to achieve a discrete, milestone breakthrough in the TMEE field.

Table 2. The top 20 institutions in terms of publication volume and their half-lives.

Rank	Affiliations	Record Count	Country	Halflife
1	Shanghai Jiao Tong Univ	155	China	7.5
2	Cent South Univ	147	China	2.5
3	Sun Yat Sen Univ	144	China	6.5
4	Nanjing Med Univ	141	China	1.5
5	Fudan Univ	138	China	7.5
6	Zhejiang Univ	129	China	12.5
7	Zhengzhou Univ	113	China	2.5
8	Huazhong Univ Sci & Technol	105	China	6.5
9	Sichuan Univ	104	China	2.5
10	Southern Med Univ	102	China	1.5
11	Shandong Univ	88	China	1.5
12	Chinese Acad Med Sci & Peking Union Med Coll	84	China	1.5
13	Univ Texas MD Anderson Canc Ctr	82	USA	8.5
14	Chinese Acad Sci	73	China	6.5
15	China Med Univ	72	China	1.5
16	Wuhan Univ	71	China	7.5
17	Harvard Med Sch	69	USA	5.5
18	Capital Med Univ	64	China	1.5
19	Tongji Univ	61	China	1.5
20	Guangzhou Med Univ	57	China	1.5



b

Top 20 Institutions with the Strongest Citation Bursts

Institutions	Year	Strength	Begin	End	1999 - 2025
Ohio State Univ	1999	5.72	**1999**	2020	
Johns Hopkins Univ	2000	9.1	**2000**	2020	
Stanford Univ	2000	4.09	**2000**	2015	
Univ Penn	2001	6.19	**2001**	2021	
Harvard Univ	2002	17.19	**2002**	2015	
Univ Toronto	2003	5.66	**2003**	2019	
Dana Farber Canc Inst	2004	9.08	**2004**	2020	
Northwestern Univ	2005	7.35	**2005**	2020	
Acad Sinica	2005	5.3	**2005**	2021	
NCI	2006	12.39	**2006**	2021	
Brigham & Womens Hosp	2008	8	**2008**	2017	
INSERM	2009	4.41	**2009**	2016	
Massachusetts Gen Hosp	2010	9.16	**2010**	2018	
Univ Texas MD Anderson Canc Ctr	2012	12.59	**2012**	2020	
Mayo Clin	2013	4.1	**2013**	2016	
Taipei Med Univ	2015	4.1	**2015**	2021	
Harvard Med Sch	2016	12.93	**2016**	2020	
NYU	2017	5.45	**2017**	2020	
Icahn Sch Med Mt Sinai	2017	5.45	**2017**	2022	
IRCCS	2018	5.96	**2018**	2021	

Figure 4. Visual Analysis of Research institutions.

(a) Institutional cluster network; (b) burst-intensity timeline of the top 20 institutions. Note: (a) Generated with VOSviewer; node colors denote clusters, node size reflects publication count, and line thickness indicates collaboration strength. (b) Generated with CiteSpace; red segments indicate burst periods of heightened activity, blue segments indicate latency or buffer periods.

3.4 Author

A total of 31,423 authors have contributed to TMEE. Table 3 lists the 20 most

prolific; all are affiliated with institutions in China or the United States. Liu Jinhui and Eyad Elkord share first place with 12 articles each. Liu's work centers on differential epigenetic-molecule expression in tumors and the development of prognostic models [6-8], whereas Elkord investigates how epigenetic modifications shape tumor immunity and drive oncogenesis [9-11]. Ogino Shuji ranks second with 11 publications, focusing on how TME alterations influence colorectal-cancer progression [12-14]. Co-authorship clustering yielded six author groups (Figure 5). The largest (red) cluster is anchored by Batra Surinder K, Huang Tao, and Huang Wei; the second largest (green) cluster revolves around Cao Ke, Chen Hao, and Chen Xi. The predominance of Chinese scholars in these clusters points to a tightly knit domestic collaboration network within the TMEE field.

Table 3. The top 20 authors in terms of the number of published papers.

Rank	Authors	Institution	Country	Documents
1	Liu, Jinhui	Cent South University	China	12
2	Eyad Elkord	Qatar Biomedical Research Institute (QBRI)	Qatar	12
3	Ogino, Shuji	Harvard Medical School	USA	11
4	Liu,Zaoqu	zhengzhou university	China	11
5	Zhang, Bixiang	Huazhong Univ Sci & Technol	China	10
6	Yu, Xianjun	Fudan University	China	10
7	Nishihara,Reiko	Harvard Medical School	USA	9
8	Seftor,Elisabeth A	Shepherd Universty	USA	9
9	Nair Varun Sasidharan	Istituto Italiano di Tecnologia	Italy	9
10	Luo,Peng	southern medical university	China	8
11	Schuller,Ulrich	Res Inst Childrens Canc Ctr Hamburg	Germany	8
12	Dietrich,D.	Univ Med Ctr Bonn UKB	Germany	8
13	Fuchs,Charles S	Yale University	USA	8
14	Postovit,Lynne-Marie	Queens University	Canada	8
15	He,Jie	Chinese Academy of Medical Sciences	China	8
16	Hendrix,M.	Shepherd University	USA	8
17	Papavassiliou,Athanasios G.	National & Kapodistrian University of Athens	Greece	7
18	Kelsey,Karl T	Brown University School of Public Health	USA	7
19	Toor,Salman M	Hamad Bin Khalifa University-Qatar	Qatar	7
20	Polyak,Kornelia	Seoul National University	South Korea	7

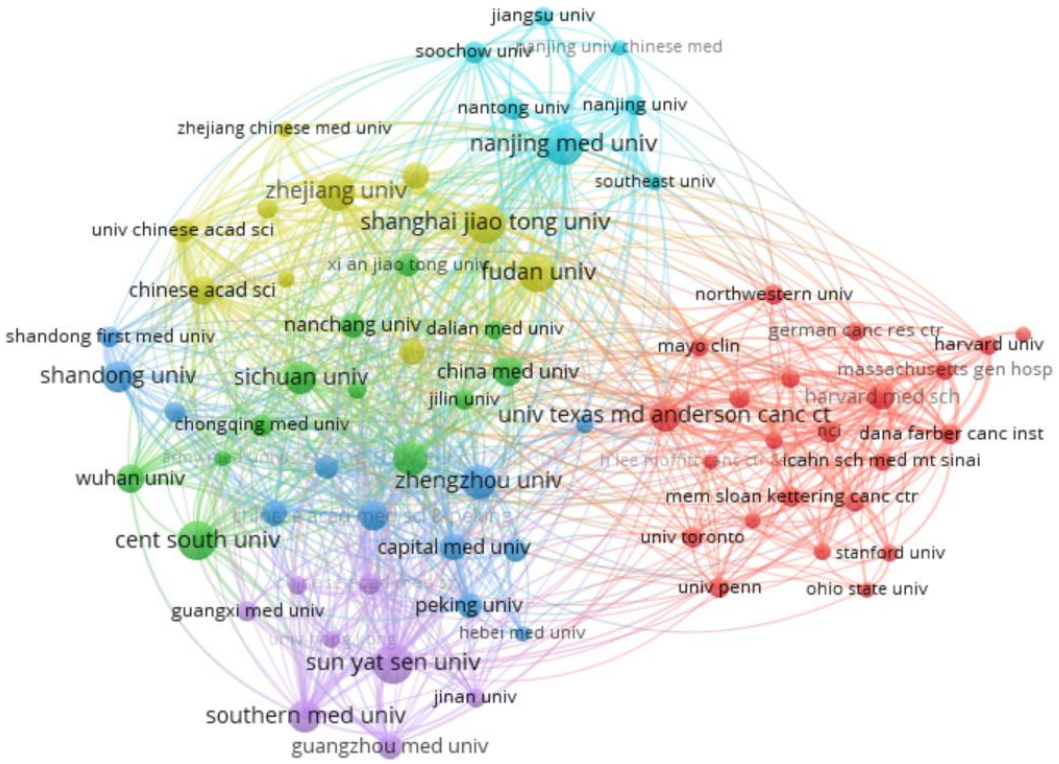


Figure 5. TMEE Author Cluster Analysis.

Note: Colors denote distinct author clusters; node size reflects publication volume, and connecting lines indicate collaborative ties.

3.5 Keywords

Table 4 lists the 20 most frequent keywords. The top three are expression (n = 1,367), tumor microenvironment (n = 1,267), and cancer (n = 875). Tumor-site—specific terms such as breast cancer, colorectal cancer, and hepatocellular carcinoma appear prominently, indicating that the microenvironment of these organs is intimately linked to tumor initiation and progression. Within the epigenetic domain, DNA methylation is among the leading keywords, underscoring its pivotal role in shaping the TME and driving tumorigenesis. At the mechanistic level, stem cells, epithelial–mesenchymal transition, metastasis, growth, and resistance recur frequently, reflecting the core biological processes underlying tumor invasion and drug resistance. Regarding therapeutic strategies, immunotherapy is repeatedly cited, confirming its emergence as a mainstream modality in contemporary oncology.

Keyword clustering (Figure 6a) further clarifies thematic relationships. The green

cluster centers on tumor immunotherapy, with core immune cells—myeloid cells, macrophages, and regulatory T cells—converging on the key immune-checkpoint ligand PD-L1. Epigenetic keywords are dispersed across clusters and encompass DNA methylation, 5-methylcytosine, histone acetylation, long non-coding RNAs, and m6A, indicating that epigenetic mechanisms permeate multiple dimensions of TMEE.

Keyword-burst analysis (Figure 6b) shows that DNA methylation is the only epigenetic term to exhibit a sustained surge, beginning in 2005 and continuing to the present. This indicates that DNA methylation is both the foundational mechanism governing TME regulation and the earliest epigenetic process to gain traction in the field. By contrast, other epigenetic keywords have yet to display comparable bursts, suggesting their associated research is still in a phase of gradual dissemination and deepening investigation.

Table 4. The top 20 keywords ranked by TMEE.

NO.	Keyword	Frequency	NO.	Keyword	Frequency
1	expression	1367	11	methylation	316
2	tumor microenvironment	1267	12	microenvironment	312
3	cancer	875	13	activation	304
4	dna methylation	727	14	metastasis	293
5	cells	619	15	growth	282
6	gene expression	532	16	survival	277
7	breast cancer	523	17	stem cells	276
8	progression	363	18	epithelial mesenchymal transition	263
9	colorectal cancer	343	19	resistance	227
10	hepatocellular carcinoma	336	20	immunotherapy	227

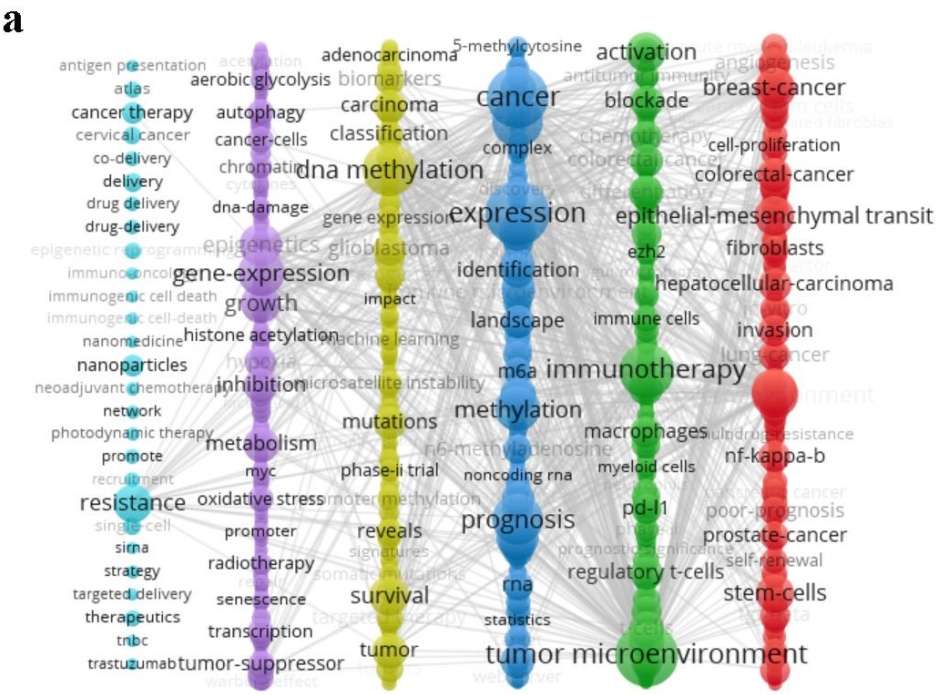


Figure 6. Visual Analysis of Keywords.

(a) Timeline-based keyword clustering. (b) Top-20 keyword burst-intensity diagram. Note: (a) Generated with VOSviewer and refined with Pajek 5.19; colors denote clusters, node size reflects frequency, and connecting lines indicate link strength. (b) Generated with CiteSpace; red segments mark burst periods of heightened attention, blue segments indicate latency or buffer phases.

3.6 Citing journals and cited journals

A total of 5,492 articles appeared in 1,012 journals. Table 5 lists the 20 most prolific; more than 90 % reside in the JCR Q1 or Q2 quartiles and their mean impact factor is 6.195, attesting to the high overall quality of TMEE research and its capacity to accurately portray how epigenetic mechanisms operate within the TME. Among these 20 journals, seven are oncology-focused, two specialize in epigenetics, and the remainder span cell and molecular biology, pharmacology, translational medicine and ageing, underscoring the multidimensional nature of epigenetic influences on tumorigenesis via the TME. The disciplinary breakdown is depicted in Figure 7a. Oncology dominates publication volume; within it, only digestive cancers are resolved to the organ-system level, indicating that epigenetically driven TME alterations are especially prominent in gastrointestinal malignancies. At the mechanistic level, the literature clusters most densely in immunology, further confirming that epigenetic TME remodelling is intimately linked to anti-tumour immunity.

To map the interplay between the knowledge frontier (citing journals) and the knowledge base (cited journals), we constructed a dual-map overlay of the journal network (Figure 7b). On the left, citing journals (frontier) are projected; on the right, cited journals (base) are shown. Node labels are derived from cluster topics extracted by the LLR algorithm. Cross-graph arcs denote citation flows, yielding a macroscopic "divergent" structure. Anchored by "Molecular Biology" and "Genetics" as the foundational knowledge base, the frontier clusters of "Immunology," "Medicine," and "Clinical Research" emerge, confirming that immunology now represents the most advanced frontier in contemporary TMEE.

Table 5. The top 20 journals in terms of publication volume.

Rank	Journal	Counts	Citation	JCR	IF
1	Frontiers in immunology	259	4018	Q1	5.7
2	Fronts in oncology	227	4952	Q2	3.5
3	Cancers	226	6100	Q1	4.5
4	International Journal of molecular sciences	143	4143	Q1	4.9
5	Frontiers in genetics	115	852	Q2	2.8
6	Scientific reports	103	1489	Q1	3.8
7	Frontiers in cell and developmental biology	101	1799	Q1	4.6
8	Cancer reasearch	63	4157	Q1	12.5
9	oncology	54	2834	Q3	2.5
10	Aging-us	52	400	Q2	3.9
11	Heliyon	50	200	Q1	3.4
12	Molecular cancer	47	5377	Q1	27.7
13	Cancer letters	47	1455	Q1	9.1
14	Frontiers in pharmacology	47	602	Q1	4.4
15	Cells	46	1347	Q2	5.1
16	Nature communications	42	2600	Q1	14.7
17	BMC cancer	42	691	Q2	3.4
18	Clinical epigenetics	75	785	Q1	4.8
19	Fronters in mlecular biosciences	73	536	Q2	3.9
20	Journal of translational medicine	69	586	Q1	6.1

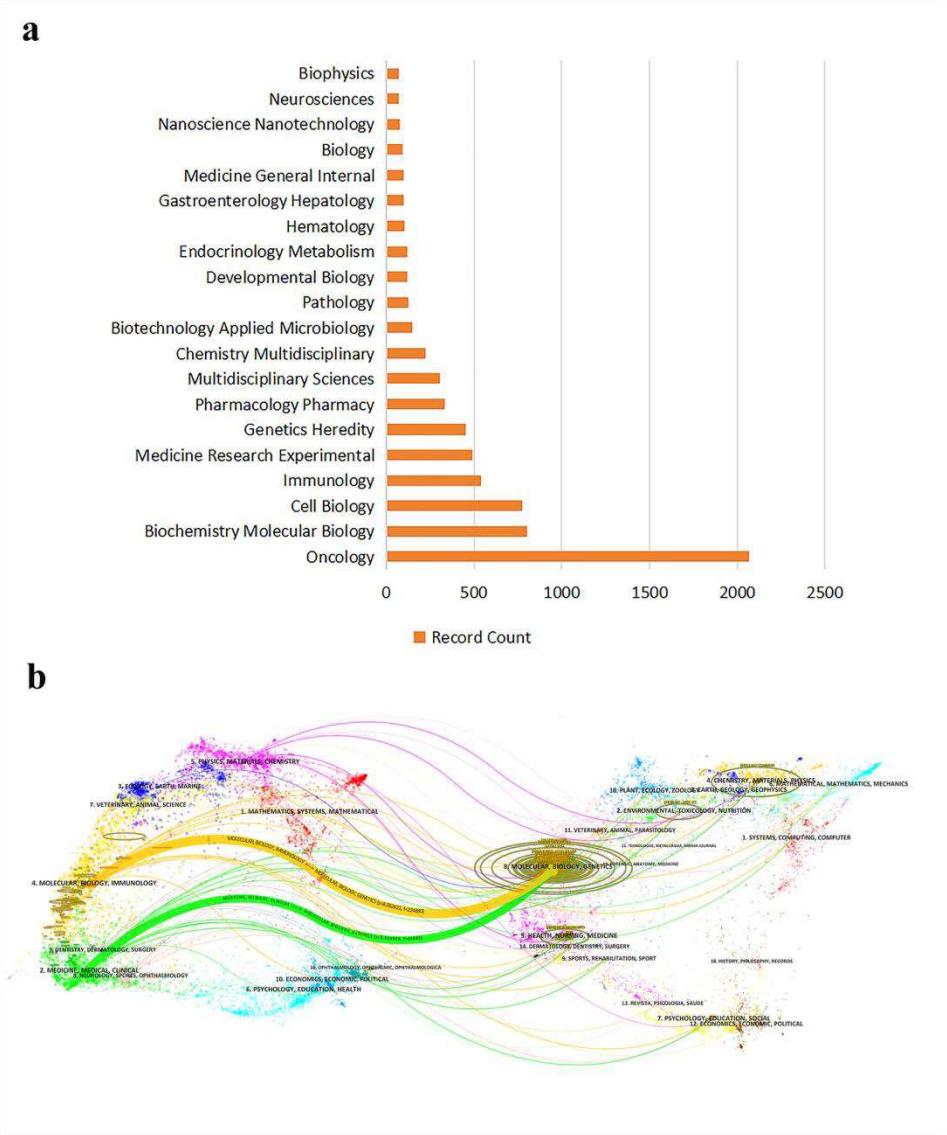


Figure 7. Analysis of Citation Journals and Cited Journals.

(a) Citation journal subject classification; (b) Superimpose the double images of the citing journal and the cited journal. Note: (b) The left side represents the clustering of cited journals; The right side represents the clustering of cited journals; The middle line indicates the reference relationship.

4. Discussion

This bibliometric study, based on 5,492 publications indexed in the Web of Science Core Collection, provides a comprehensive overview of the current research landscape in TMEE. By integrating co-authorship, co-occurrence, clustering, and burst analysis, we systematically examine the characteristics of this rapidly evolving field in terms of knowledge structure, collaboration patterns, and thematic evolution.

TME research can be traced back to 1999, when Spanish scholar Alvarez, A first reported differences in differentiation between primary subcutaneous/splenic tumors and liver/lung metastases of CE44 teratocarcinoma cells, providing the earliest indication that organ microenvironments and epigenetics jointly determine tumor cell fate [15]. In the same year, German scholar Jurianz, K formally introduced the concept of "tumor microenvironment" [16]. The field remained in a period of slow development thereafter until 2019, when it entered a phase of rapid expansion—this leap being closely tied to advances in epigenetic technologies [17]. Currently, research in this area has entered a stage of stable growth. China (2,825 papers, 51.44%) and the United States (1,346 papers, 24.51%) are the core drivers of progress in this field. The U.S. holds the highest centrality score (0.36), highlighting its dominant position in TME research. Eighteen of the top 20 most productive institutions are from China; however, institutional collaboration networks reveal limited international cooperation among Chinese institutions, which explains why China produces the highest number of publications yet lacks significant centrality.

The keyword clustering and emergent analysis show that DNA methylation is the earliest and most deeply studied epigenetic regulatory mechanism in research. Studies have shown that DNA methylation reprogramming not only participates in the regulation of gene expression in tumor cells, but also can promote the formation of an immunosuppressive microenvironment by influencing the functions of immune cells and stromal cells. Targeting DNA methylation can promote the transformation of "cold tumors" to "hot tumors" . From the chronological order of the appearance of keywords, the research hotspots of TMEE have shifted from DNA methylation to histone modification, non-coding RNA, and RNA modification. M6A modification is currently the research hotspot and trend. It is worth noting that "EZH2", as the core histone methyltransferase of the PRC2 complex, shows a relatively high research interest in keyword clustering analysis. In recent years, it has been discovered that EZH2 not only promotes tumor progression by catalyzing H3K27me3-mediated silencing of tumor suppressor genes, but also plays a key role in the remodeling of the tumor immune microenvironment [18,19]. EZH2 can inhibit the expression of antigen presentation-related genes, reduce the immunogenicity of tumor cells, and promote immune escape by regulating the functions of regulatory T cells (Treg), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) [20,21]). In addition, EZH2 is closely related to PD-L1 expression regulation and immune checkpoint inhibitor

resistance, making it an important bridge connecting epigenetic regulation and tumor immunotherapy [22,23]. With the continuous development of the combined strategy of EZH2 inhibitors and immunotherapy, EZH2 is expected to become an important intervention target for targeted treatment of tumor microenvironment in the future [18].

The keyword analysis reveals that "stem-cells", "myeloid cells", "macrophages" and "regulatory T-cells" are the most highly regarded cell types in the tumor microenvironment (TME), reflecting that the research focus in this field is gradually shifting from tumor cells themselves to the dynamic interactions between tumors and immune cells. Recent studies have shown that these cells collectively form an important component of the tumor immune suppression network [24,25]. Among them, cancer stem cells (CSCs) not only maintain tumor heterogeneity and treatment resistance but also can remodel the immune microenvironment by secreting chemokines and cytokines [26]; while myeloid cells, tumor-associated macrophages (TAMs), and regulatory T-cells (Tregs) support tumor progression by promoting immune escape and maintaining a chronic inflammatory state[27,28]). Moreover, an increasing amount of evidence indicates that there is a bidirectional regulatory relationship between cancer stem cells and the immunosuppressive microenvironment, jointly promoting tumor progression and treatment tolerance [29]. With the development of single-cell sequencing and spatial transcriptomics techniques, researchers have gradually recognized that the complex spatiotemporal interactions between different cell populations are important factors determining tumor progression and immune treatment response [30,31]). These techniques not only enhance the understanding of tumor cell heterogeneity but also reveal the organizational patterns and functional differentiation of immune cells and stromal cells in the spatial dimension, providing a new research perspective for deciphering the dynamic regulatory mechanisms of the tumor microenvironment. It is worth noting that epigenetic reprogramming is considered an important mechanism driving the transformation of immune cell states. DNA methylation, histone modifications, and non-coding RNAs can shape the immunosuppressive TME by regulating macrophage polarization, myeloid cell differentiation, and Treg stability[29,32]. Moreover, abnormal DNA methylation not only affects the transcriptional program of tumor cells but also reshapes the tumor immune microenvironment, thereby influencing immune surveillance and treatment response [18]. Key epigenetic regulatory factors such as EZH2, DNMTs, and HDACs not only participate in the determination of immune cell fate but also affect antigen

presentation, immune checkpoint expression, and T cell infiltration, thereby regulating the response of tumors to immunotherapy [18-20]. Recent reviews have further pointed out that epigenetic regulation has become an important bridge connecting tumor development, immune microenvironment remodeling, and precise treatment [16].

"Immunotherapy" not only ranks high among the frequently used keywords, but also appears in the knowledge frontier cluster, indicating that the research on TME and epigenetics is gradually moving from mechanism analysis to clinical translation. In recent years, the widespread application of immune checkpoint inhibitors (immune checkpoint inhibitors, ICIs) has significantly improved the prognosis of patients with various malignant tumors, but treatment response heterogeneity and acquired resistance remain the main challenges limiting their efficacy. By combining the keyword evolution results of this study, it can be found that epigenetic regulatory factors such as DNA methylation, EZH2, non-coding RNA, and m6A show a significant cross-trend with immunotherapy-related research, suggesting that epigenetic abnormalities may be important determinants affecting the immune therapy response. It has been discovered that DNA demethylating drugs can induce the expression of endogenous retroviruses (endogenous retroviruses, ERVs), trigger the "viral mimicry" effect and activate the type I interferon signal, thereby enhancing the immunogenicity of tumor cells [33]. In addition, abnormal DNA methylation and chromatin remodeling can also lead to the downregulation of MHC-I expression and antigen presentation disorders, thereby promoting immune escape and ICIs resistance [32]. At the same time, the prominent performance of "PD-L1" in the clustering analysis further reflects that the current research focus has shifted to the regulatory mechanisms of immune escape. The traditional view holds that PD-L1 mainly serves as an important biomarker for immune checkpoint therapy, but recent studies have found that PD-L1 expression is subject to multiple levels of epigenetic regulation and is closely related to the state of the tumor immune microenvironment. The H3K27me3 modification mediated by EZH2 can inhibit the expression of antigen presentation-related genes and participate in the remodeling of the PD-L1-related signaling network[18]; in addition, m6A RNA modification has been confirmed to affect the immune therapy response by regulating the stability and translation efficiency of PD-L1 mRNA [34]. Therefore, PD-L1 may be an important hub connecting the intrinsic epigenetic state of the tumor and the external immune microenvironment. It is worth noting that single-cell sequencing and spatial transcriptomics evidence indicates that there are significant differences in epigenetic

states and PD-L1 expression patterns in different regions and cell subpopulations within the same tumor, and this spatial heterogeneity is closely related to the immune therapy response [30]. Therefore, in-depth analysis of the underlying epigenetic regulatory network and cell state transition mechanism is the key to tumor immunotherapy.

Although this study has comprehensively revealed the current research status and development trends in the field of tumor microenvironment and epigenetics, it still has certain limitations. Firstly, this study was conducted based on the Web of Science Core Collection (WoSCC) database, and some relevant literature that was not included in this database might not have been covered in the research scope. Secondly, since bibliometric analysis relies on the publication time and citation status of the literature, important research published in recent years may not have accumulated sufficient citation volume, and their academic influence has not been fully reflected. In future research, we will continue to improve.

5. Conclusion

This study mapped the research landscape of tumor microenvironment (TME) and epigenetics over the past two decades. The findings show a clear shift from basic epigenetic mechanisms toward immune regulation, cellular heterogeneity, and therapeutic relevance. A key trend is the growing convergence of epigenetics and tumor immunology. The prominence of immune-related cells and immunotherapy-related topics suggests that current research increasingly focuses on how epigenetic programs shape interactions within the TME and influence tumor progression and treatment response. Future studies will likely benefit from single-cell sequencing, spatial omics, and multi-omics integration to better define the spatiotemporal complexity of epigenetic regulation. Rather than identifying more regulators alone, the main challenge is to understand how epigenetic networks coordinate multicellular interactions and antitumor immunity. Overall, epigenetics is emerging as an important bridge between tumor biology, immune regulation, and precision oncology.

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