

# Evolution of Glioma and Hypoxia Research (2005–2025): A Bibliometric Analysis from Molecular Mechanisms to Tumor Microenvironment and Translational Medicine

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# Evolution of Glioma and Hypoxia Research (2005-2025): A Bibliometric Analysis from Molecular Mechanisms to Tumor Microenvironment and Translational Medicine

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**Keywords:** glioma; hypoxia; tumor microenvironment; bibliometrics; immunoregulation

## Abstract

**Background:** Gliomas are prevalent, highly invasive central nervous system malignancies. The intratumoral hypoxic microenvironment, primarily mediated by hypoxia-inducible factor (HIF) signaling, orchestrates therapeutic resistance and malignant progression, representing a major clinical bottleneck. This study systematically maps the global research landscape and frontier trends concerning glioma and hypoxia from 2005 to 2025.

**Methods:** English-language original articles published between 2005 and 2025 were retrieved from the Web of Science Core Collection. After rigorous screening, 1,983 valid records were incorporated. Multidimensional bibliometric analyses encompassing publication chronology, global contributions, and keywords were conducted utilizing R, VOSviewer, and CiteSpace.

**Results:** The dataset spanned 69 countries and 2,283 institutions. China and the United States emerged as dual-core leaders; China ranked first in publication volume, hosting eight of the top ten most productive institutions, while the US anchored the international collaboration network. Cancer Research was identified as the premier journal. Keyword analysis revealed a profound paradigm shift from basic single-pathway exploration to multi-omics translational medicine. Specifically, the tumor immune microenvironment, macrophage polarization, epigenetic lactylation, and nanomedicine have crystallized as prominent recent hotspots.

**Conclusions:** Research on glioma hypoxia is rapidly advancing toward multidisciplinary clinical translation. Future frontiers will be heavily driven by AI-assisted non-invasive radiomics, microenvironment-remodeling smart nanomaterials, and hypoxia-targeted combination immunotherapies. This comprehensive study provides critical bibliometric insights to navigate future neuro-oncological therapeutics.

## 1. Introduction

As the most frequently occurring primary malignancy of the central nervous system (CNS), glioma is associated with persistently high incidence and mortality rates, representing one of the most formidable challenges in contemporary neuro-oncology [1-6]. Gliomas exhibit profound biological heterogeneity and extreme invasiveness. Their diffuse, infiltrative growth pattern obscures distinct tumor margins [7-10], rendering complete biological eradication via surgical resection virtually impossible and post-operative recurrence almost inevitable [11]. According to the World Health Organization (WHO) pathological classification, gliomas are stratified into grades I through IV [12, 13]. While lower-grade gliomas (grades I–II) exhibit relatively indolent growth, they

inherently possess the malignant potential for anaplastic progression to higher grades [14-16]. For high-grade gliomas, exemplified by glioblastoma (GBM, WHO grade IV), the clinical prognosis remains dismal; the median survival time is merely 12.1–14.6 months, accompanied by an exceptionally low 5-year survival rate [5, 7, 17-20]. This bleak outcome is intricately linked to their intrinsic biological hallmarks: uncontrolled cellular proliferation, cross-barrier invasive capabilities, and profound resistance to conventional chemo-radiotherapy [19, 21-25].

Emerging evidence over recent years has elucidated that the malignant phenotype of glioma is not solely dictated by intrinsic somatic mutations but is also heavily orchestrated by its complex surrounding microenvironment, wherein hypoxia acts as a core stressor driving tumor evolution [7, 26-31]. Because the exponential proliferation of neoplastic cells vastly outpaces the lagging rate of functional neoangiogenesis, the intratumoral core remains subjected to a chronic, extreme state of hypoxic stress [22, 30, 32-34]. This hypoxic microenvironment extends beyond being a mere byproduct of tumor growth; it is a primary selective pressure accelerating malignant progression [27-29]. At the molecular level, hypoxia-inducible factors (HIFs) function as the master regulatory hubs for oxygen sensing, triggering a cascade of survival adaptations via profound transcriptional reprogramming [14, 21, 35, 36]. Driven by hypoxia, stabilized HIFs translocate into the nucleus, bind to hypoxia-response elements (HREs) in target gene promoters, and initiate pro-angiogenic cascades—such as vascular endothelial growth factor (VEGF) signaling [37]—in a compensatory attempt to restore oxygen and nutrient supply [38, 39]. However, the pathophysiological impact of hypoxia far exceeds angiogenesis [40]. It fundamentally induces metabolic reprogramming (the "Warburg effect"), empowering tumor cells to acquire energy in harsh environments via upregulated glycolysis, which is inherently accompanied by the accumulation of acidic metabolites [38, 41]. Furthermore, hypoxia actively maintains the self-renewal and multipotent differentiation capacities of glioma stem cells (GSCs) by forming specialized hypoxic niches, serving as a biological "safe haven" for tumor recurrence and chemo-radiation resistance [42, 43]. More critically, hypoxia remodels the local immune landscape. It upregulates immune checkpoint molecules such as PD-L1 [44, 45], recruits myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [46-48], and severely impairs the cytotoxic functions of effector T cells and natural killer (NK) cells [44, 49]. Consequently, a dense immunosuppressive shield is established, allowing the tumor to evade host immune surveillance [26, 50, 51].

Despite a surge in hypoxia-related glioma research over the past two decades—with investigations scaling from single-molecule pathways to multi-omics systems biology—the field still lacks a comprehensive, data-driven bibliometric review based on authoritative databases. Given the exponential growth of scientific literature and the rapid iteration of modern biotechnologies such as single-cell RNA sequencing (scRNA-seq)

and spatial transcriptomics, accurately deciphering the global research landscape, developmental trajectories, and frontier hotspots has become a crucial imperative. Bibliometric analysis, as a rigorous quantitative methodology integrating mathematics and statistics, enables the intuitive visualization of research trends via scientific knowledge mapping. It quantitatively evaluates the academic impact of nations, institutions, and scholars, ultimately unmasking paradigm shifts at the scientific vanguard. Therefore, leveraging the Web of Science Core Collection, the present study conducts a comprehensive bibliometric analysis of the glioma and hypoxia research domain spanning 2005 to 2025, bridging macro-level scientific collaborative patterns with microscopic molecular heterogeneities to guide future translational interventions.

## **2. Materials and Methods**

### **2.1 Data Acquisition and Search Strategy**

The Web of Science (WoS) Core Collection is internationally recognized for its reliability and exhaustive coverage of high-impact academic literature, rendering it the optimal database for bibliometric analysis. Relevant literature was retrieved from this database to construct the analytical dataset. To ensure data accuracy and consistency, and to circumvent potential biases introduced by dynamic database updates, a comprehensive literature retrieval and data export were executed on a single day (February 15, 2026). The search encompassed literature published between January 1, 2005, and December 31, 2025. The precise search strategy applied was: "glioma AND hypoxia OR hypoxia microenvironment AND HIF-1 $\alpha$ ". To minimize selection bias, explicit refinement criteria were enforced: (1) document type was strictly limited to "Article"; (2) the publication language was restricted to English; and (3) the temporal bounds were set from January 1, 2005, to December 31, 2025. Following these criteria, a total of 1,983 valid original research articles were secured for detailed downstream analysis. The comprehensive literature screening process is depicted in Figure 1

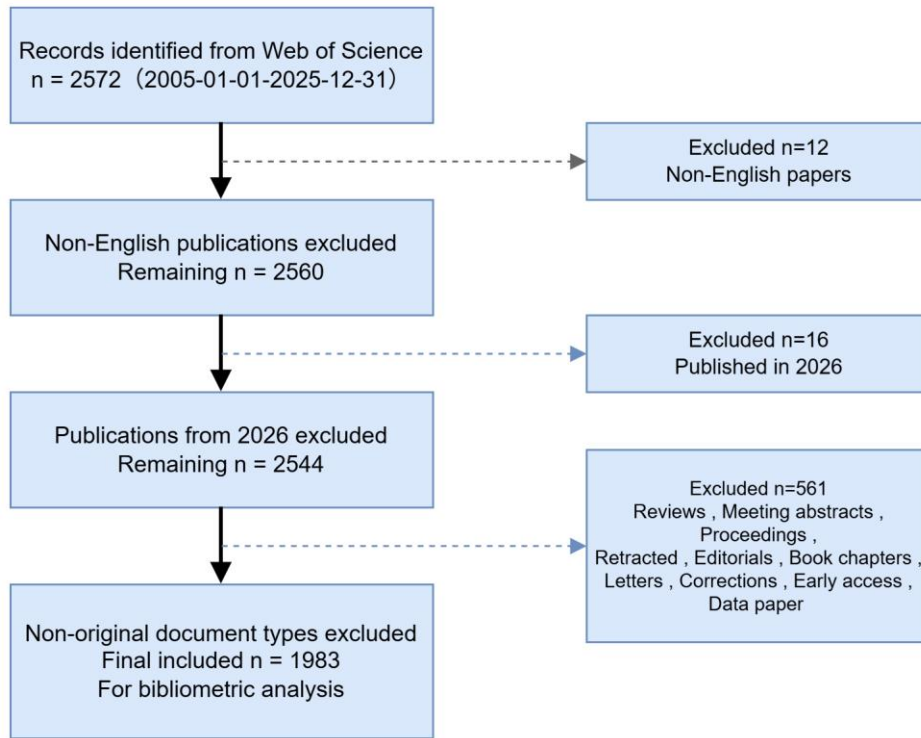


**Figure 1**Flowchart of literature search strategy and selection process. This diagram delineates the systematic screening methodology employed to retrieve relevant articles from the Web of Science Core Collection (2005–2025). The process highlights rigorous inclusion/exclusion criteria, resulting in a final dataset of 1,983 valid original research articles for bibliometric analysis.

## 2.2 Data Analysis

To achieve a profound analytical dissection of the dataset, we deployed the "bibliometrix" package within the R programming environment (version 4.3.2). This specialized R package facilitates the evaluation of publication outputs stratified by countries, institutions, journals, and authors; measures the density of international collaborations; and identifies dominant research trends via keyword frequency mapping. To complement this, we integrated two advanced visual analytics software tools: CiteSpace (version 6.2.R6) and VOSviewer (version 1.6.20). CiteSpace, a Java-based citation visualization platform equipped with robust data processing capabilities, efficiently translates massive volumes of bibliographic metadata into intuitive citation network graphs. Utilizing CiteSpace, we precisely screened and deeply investigated keywords and references demonstrating significant citation bursts, thereby uncovering underlying academic dynamics and evolving research hotspots. VOSviewer, developed by Nees Jan van Eck and Ludo Waltman in 2009, excels in the spatial mapping of bibliometric networks, offering a clear visual representation of core entities such as authors, cited authors, and research institutions. Through VOSviewer, we visually

assessed the collaborative associations among global research entities, providing robust empirical support for understanding the academic landscape. The methodological innovation of this study lies in the synergistic integration of CiteSpace and VOSviewer, enabling a multidimensional, systematic, and highly granular evaluation of the research field. This multi-tool framework ensures a comprehensive grasp of developmental lineages, research trends, and potential frontier directions, providing solid theoretical and data-driven support for future neuro-oncological endeavors.

### 3. Results

#### 3.1 Analysis of Publication Quantity and Temporal Trends

Based on the 1,983 rigorously screened English research articles from the WoS Core Collection, this study systematically quantified the annual publication distribution in the global glioma and hypoxia domain from 2005 to 2025 and mapped the corresponding temporal trends (Figure 2).

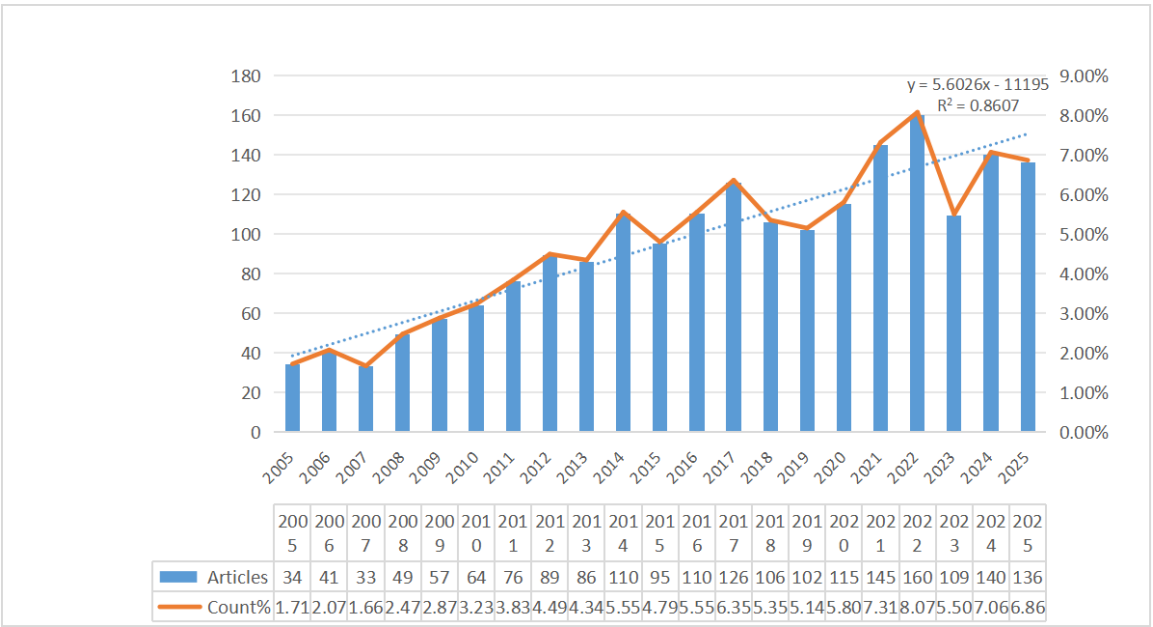


**Figure 2**Flowchart of literature search strategy and selection process. This diagram delineates the systematic screening methodology employed to retrieve relevant articles from the Web of Science Core Collection (2005-2025). The process highlights rigorous inclusion/exclusion criteria, resulting in a final dataset of 1,983 valid original research articles for bibliometric analysis.

The global research pattern was characterized by dual-core leadership of China and the United States, with strong contributions from European countries and rapid progress in the Asia-Pacific region, and international collaboration has become a key driver of scientific innovation. China ranked first with 742 articles (37.42%), followed by the United States with 407 (20.52%) and Germany with 141 (7.11%). Together, China and the USA accounted for 57.94% of the total publications, forming the dominant core of

this field. In terms of academic influence, China achieved the highest average citations per article (80.80, total 32,890), indicating wide international recognition of its research quality. The United States contributed 23,427 total citations and maintained a leading role in basic research regarding glioma stem cells and the hypoxic microenvironment. Germany, South Korea, and France also showed high average citations (>40), with South Korea reaching 72.60 per article, reflecting outstanding quality in specialized subfields. European countries exhibited higher international collaboration activity, with Germany (39.72%) and the United Kingdom (37.50%) as leaders. The global collaboration network was centered on North America, East Asia, and Europe. The partnership between China and the USA was the strongest (64 joint publications), followed by USA-Germany (29), USA-UK (26), and USA-Japan (21). China also maintained close cooperation with Germany (13). Such cross-border collaborations integrated complementary strengths: the USA in fundamental innovation, China in translational research, and Europe in detailed mechanistic studies, which effectively accelerated research progress and clinical translation.

### 3.2 Country and Region Distribution

Literature pertaining to glioma and hypoxia spans 69 countries or regions globally, comprehensively encapsulating the premier research forces in this field. We conducted a systematic bibliometric evaluation of publication scale, academic impact, and international collaboration dynamics across various nations. Key metrics (publication volume, total citations, and collaboration percentages) for the top 10 most productive nations are detailed in Table 1,

| Country        | Articles | Articles % | SCP | MCP | MCP % | TC    | Average Article Citations |
|----------------|----------|------------|-----|-----|-------|-------|---------------------------|
| CHINA          | 742      | 37.42      | 661 | 81  | 10.92 | 32890 | 80.80                     |
| USA            | 407      | 20.52      | 311 | 96  | 23.59 | 23427 | 31.60                     |
| GERMANY        | 141      | 7.11       | 85  | 56  | 39.72 | 6466  | 45.90                     |
| JAPAN          | 94       | 4.74       | 81  | 13  | 13.83 | 3076  | 43.90                     |
| ITALY          | 70       | 3.53       | 55  | 15  | 21.43 | 3061  | 32.60                     |
| FRANCE         | 68       | 3.43       | 46  | 22  | 32.35 | 2831  | 41.60                     |
| KOREA          | 58       | 2.92       | 46  | 12  | 20.69 | 1959  | 72.60                     |
| INDIA          | 50       | 2.52       | 39  | 11  | 22.00 | 1802  | 58.10                     |
| UNITED KINGDOM | 40       | 2.02       | 25  | 15  | 37.50 | 1634  | 40.90                     |
| CANADA         | 31       | 1.56       | 21  | 10  | 32.26 | 1574  | 27.10                     |

**Table 1** Metrics of publications from the top 10 countries in the area of glioma and hypoxia research.

while the international collaboration network and high-frequency associations are visualized in Figure 3.

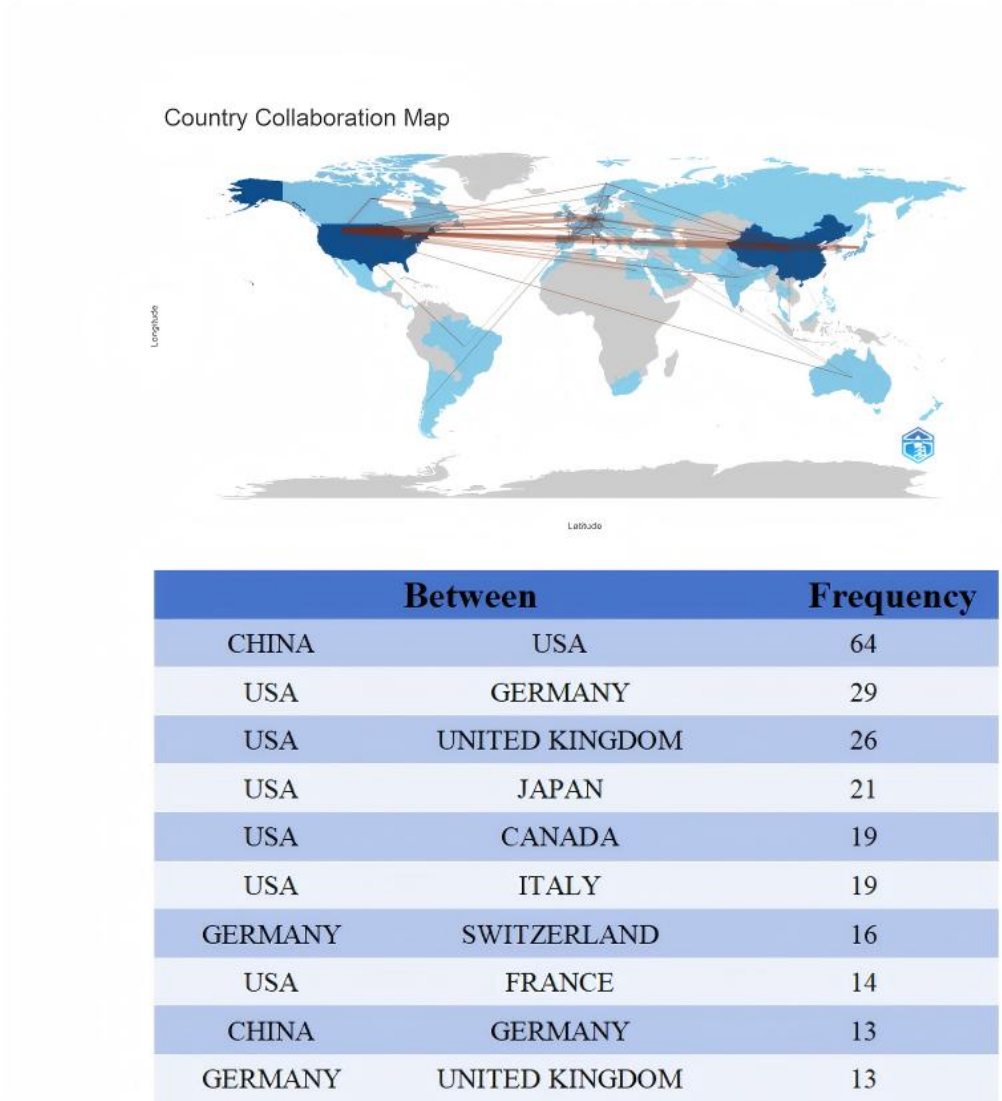


**Figure 3**Analysis of the collaborative network between glioma and hypoxia related literature sources in different countries.

The macro-level global landscape reveals a distinct paradigm: "dual-core leadership by China and the United States, high-quality concentrated efforts by multiple European nations, rapid emergence in the Asia-Pacific region, and progressively deepening transnational synergy." International academic collaboration has undeniably become the primary catalyst for innovative development. In terms of publication volume, China, the United States, and Germany constitute the global top tier. China firmly secured the leading position with 742 publications (37.42% of the total included literature),

functioning as the largest research entity in this domain. The United States ranked second with 407 articles (20.52%), followed by Germany with 141 articles (7.11%). Remarkably, the combined output of China and the US accounted for 57.94% of global publications, establishing them as the absolute core drivers of the field. Japan, Italy, France, South Korea, and other nations followed, forming a well-stratified global research hierarchy. Regarding academic influence, China amassed 32,890 total citations (TC), achieving an average of 80.80 citations per article—the highest among the top 10 nations. This metric affirms that China's research outcomes are not only massive in scale but also highly recognized for their academic quality by the international community. The United States accumulated 23,427 total citations, averaging 31.60 citations per article. Supported by robust funding, elite research clusters, and exceptional talent pools, the US continuously delivers groundbreaking foundational discoveries, particularly regarding the interaction mechanisms between glioma stem cells and the hypoxic niche. European nations like Germany and France maintained excellent metrics, while South Korea exhibited an impressive average of 72.60 citations per article; despite a smaller publication volume, the high caliber of its individual studies has established unique advantages in specialized sub-disciplines. Analysis of international collaboration ratios demonstrated that Germany and the United Kingdom possessed high collaboration rates of 39.72% and 37.50%, respectively, reflecting a generally higher level of cooperative engagement among European nations. The geographic visualization (Figure 3) clearly illustrates a global collaborative network anchored by three core hubs: North America, East Asia, and Europe. The collaboration frequency between China and the US peaked at 64, ranking first globally and highlighting the profound depth and breadth of scientific synergy between the two nations. Other high-frequency associations predominantly utilized the US as a central hub (e.g., US-Germany: 29; US-UK: 26; US-Japan: 21). Concurrently, Sino-German collaborations reached 13, indicating deepening ties with European vanguards. Transnational synergy effectively leverages complementary strengths: the US excels in foundational theoretical innovation, China advances rapidly in translational medicine via expansive clinical resources, and Europe contributes precise mechanistic elucidations, collectively accelerating outcome generation and the clinical translation process.

### **3.3 Author Analysis**

Over the 20-year span (2005–2025), a total of 11,154 contributing authors and 35,853 cited authors participated in global glioma and hypoxia research, making systematic contributions to theoretical breakthroughs, technological innovations, and clinical translations. Utilizing VOSviewer, this study generated an author co-authorship map and a co-citation network (Figure 4) to systematically dissect the core investigator groups across three dimensions: publication output, academic impact, and collaborative

associations.

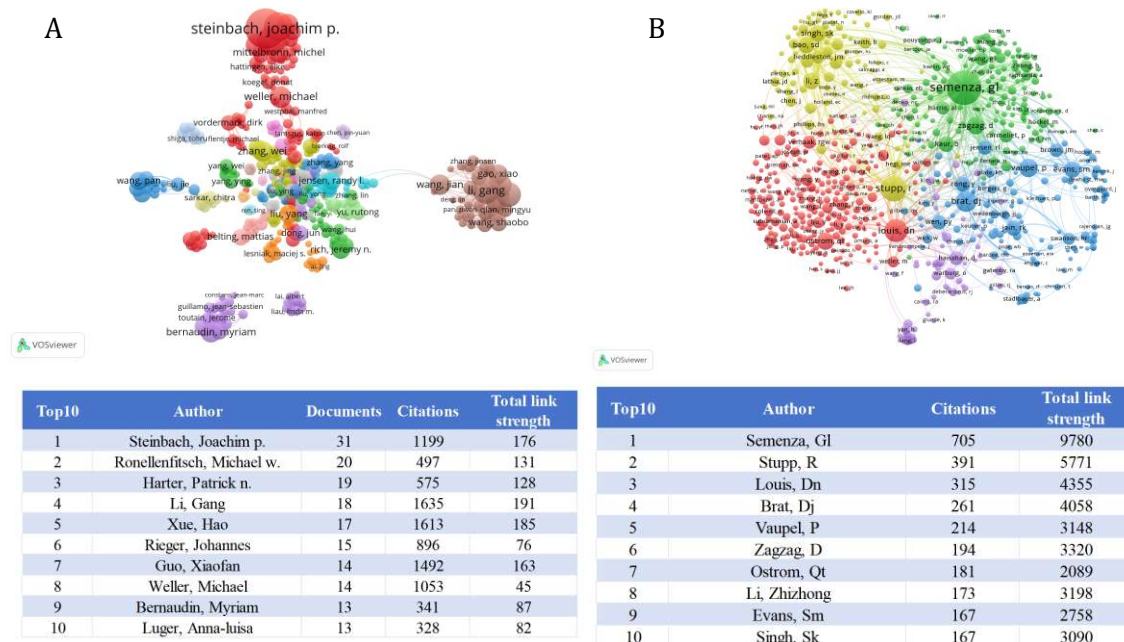


**Figure 4(A) Author visualization: Node size represents the number of articles. (B) Co-citation author analysis chart, where the size of nodes represents the number of repetitions.**

Figure 4A displays the co-authorship visualization, where node size directly corresponds to publication volume and edge thickness denotes collaboration strength. Applying a threshold of at least 3 relevant articles per author isolated 654 core high-yield investigators. Statistical results show that Steinbach, Joachim P. ranks first with 31 publications, 1,199 total citations, and a total link strength of 176, making him the scholar with the largest publication scale and the strongest centrality in the collaborative network. Ronellenfitsch, Michael W. ranks second (20 publications, 497 citations, link strength 131), and Harter, Patrick N. ranks third (19 publications, 575 citations, link strength 128). Furthermore, scholars such as Li, Gang, Xue, Hao, and Guo, Xiaofan entered the global top 10 high-yield authors, forming stable research outputs while maintaining high academic influence and collaborative activity. Figure 4B illustrates the author co-citation analysis, wherein node size corresponds to total co-citation frequency—measuring the scholar’s academic influence and theoretical foundational role in the field. Applying a minimum threshold of 15 co-citations isolated 646 highly influential scholars. Semenza, GL ranks first globally with 705 co-citations and a link strength of 9,780. As the most academically leading core scholar, his findings constitute an essential theoretical foundation. Stupp, R ranks second (391 co-citations, link strength 5,771), and Louis, DN ranks third (315 co-citations, link strength 4,355); their paradigm-shifting outcomes are universally referenced. Additionally, scholars such as Brat, DJ, Vaupel, P, and Li, Zhizhong populated the top 10, providing key support for mechanistic exploration and translational initiatives. The overarching collaborative landscape reveals a highly interconnected, multi-center network. Core scholars function as pivotal hubs, linking

cross-disciplinary teams to tackle key therapeutic challenges—such as HIF-1 $\alpha$  targeted drug development, hypoxic microenvironment regulatory mechanisms, and targeted therapy strategies for glioma. Through collaborative models characterized by technology sharing, resource integration, and complementary expertise, they act as the primary engine sustaining continuous innovation in the field.

### 3.4 Institution Analysis

A total of 2,283 global research institutions contributed to academic outputs concerning glioma and hypoxia. We performed a rigorous bibliometric assessment of their publication scale, academic influence, and collaborative topologies. Key metrics for the top 10 core institutions are summarized in Table 2, while the institutional collaboration network is visualized in Figure 5.

| Top10 | Organization                                  | Articles | Citations | Country |
|-------|-----------------------------------------------|----------|-----------|---------|
| 1     | Soochow University                            | 43       | 1358      | China   |
| 2     | Shanghai Jiao Tong University                 | 42       | 1338      | China   |
| 3     | Nanjing Medical University                    | 39       | 1381      | China   |
| 4     | Shandong University                           | 37       | 2236      | China   |
| 5     | Capital Medical University                    | 36       | 883       | China   |
| 6     | Huazhong University of Science and Technology | 35       | 951       | China   |
| 7     | University of Texas MD Anderson Cancer Center | 35       | 2761      | America |
| 8     | German Cancer Consortium (DKTK)               | 31       | 812       | Germany |
| 9     | Chinese Academy of Sciences                   | 30       | 2480      | China   |
| 10    | Fudan University                              | 29       | 1704      | China   |

**Table 2**Top 10 institutions with the highest number of publications.

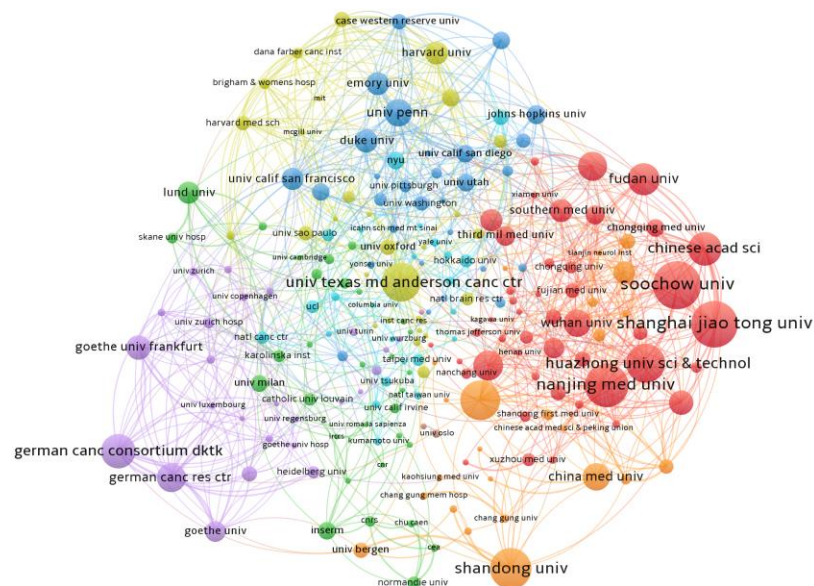


**Figure 5** Institutional co-occurrence chart.

The top 10 institutions collectively published 289 articles, encompassing 18.0% of the total dataset, thereby serving as the vanguard driving technological innovation. Soochow University ranked first globally with 43 publications and 1,358 total citations. Shanghai Jiao Tong University and Nanjing Medical University followed closely with 42 and 39 publications (1,338 and 1,381 citations, respectively). The University of Texas MD Anderson Cancer Center tied for sixth with 35 publications but amassed a staggering 2,761 total citations, making it the institution with the highest per-article impact among the top 10. Its paradigm of generating high-value, translational discoveries provides critical directional benchmarks for global researchers. Strikingly, 8 of the top 10 most productive global institutions are situated in China. This finding powerfully underscores the systematic, scaled research dominance achieved by Chinese academic institutions, confirming that China's scientific investments in the glioma microenvironment have definitively entered the global premier tier. This shift successfully disrupts the historical monopoly held by Western nations in neuro-oncology, infusing the global community with substantial clinical data and research vigor. In the institutional collaboration map, where node size correlates with publication volume and edge thickness denotes partnership intensity, Soochow University, Shanghai Jiao Tong University, and Nanjing Medical University operate as central hubs, maintaining expansive ties with international and domestic entities. The global institutional landscape is characterized by a dense, cross-regional collaborative network. Cross-institutional synergistic innovation is the core driver of modern scientific progress. This framework eradicates isolated resource silos, facilitating a seamless pipeline from fundamental target discovery at research institutes to clinical validation in affiliated hospitals. This collaborative continuum significantly compresses the translational cycle, providing an indispensable foundation for multinational clinical trials and novel combinational drug development.

### **3.5 Journal Analysis**

Academic journals serve as the primary conduits for knowledge dissemination and scholarly discourse. Analyzing their publication distribution, citation impact, and co-citation characteristics accurately delineates the authoritative publication venues and the pedigree of knowledge transfer in glioma research. The 1,983 valid articles were distributed across 628 diverse academic journals. Statistical profiles of the top 10 journals by publication volume and the top 10 high-impact journals by total citations are presented

in Table 3 and Table 4,

| Top10 | Sources                                     | Articles | JCR(2023) |
|-------|---------------------------------------------|----------|-----------|
| 1     | PLOS ONE                                    | 53       | Q2        |
| 2     | ONCOTARGET                                  | 46       | Q1        |
| 3     | NEURO-ONCOLOGY                              | 44       | Q1        |
| 4     | INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES | 41       | Q1        |
| 5     | JOURNAL OF NEURO-ONCOLOGY                   | 39       | Q2        |
| 6     | INTERNATIONAL JOURNAL OF ONCOLOGY           | 38       | Q1        |
| 7     | CANCER RESEARCH                             | 35       | Q1        |
| 8     | CANCERS                                     | 35       | Q2        |
| 9     | SCIENTIFIC REPORTS                          | 35       | Q1        |
| 10    | ONCOLOGY REPORTS                            | 31       | Q2        |

**Table 3**The top ten journals with the most sources of literature.

| Top10 | Source                                                                          | Total Ctiations | JCR (2023) |
|-------|---------------------------------------------------------------------------------|-----------------|------------|
| 1     | CANCER RESEARCH                                                                 | 5256            | Q1         |
| 2     | NEURO-ONCOLOGY                                                                  | 3712            | Q1         |
| 3     | CANCER CELL                                                                     | 3124            | Q1         |
| 4     | PLOS ONE                                                                        | 2781            | Q2         |
| 5     | PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA | 2761            | Q1         |
| 6     | ONCOGENE                                                                        | 2446            | Q1         |
| 7     | ONCOTARGET                                                                      | 1868            | Q1         |
| 8     | JOURNAL OF NEURO-ONCOLOGY                                                       | 1715            | Q2         |
| 9     | CELL STEM CELL                                                                  | 1657            | Q1         |
| 10    | INTERNATIONAL JOURNAL OF ONCOLOGY                                               | 1548            | Q1         |

**Table 4**The top ten journals with the most citations.

respectively. The journal co-citation network is visualized in Figure 6 .

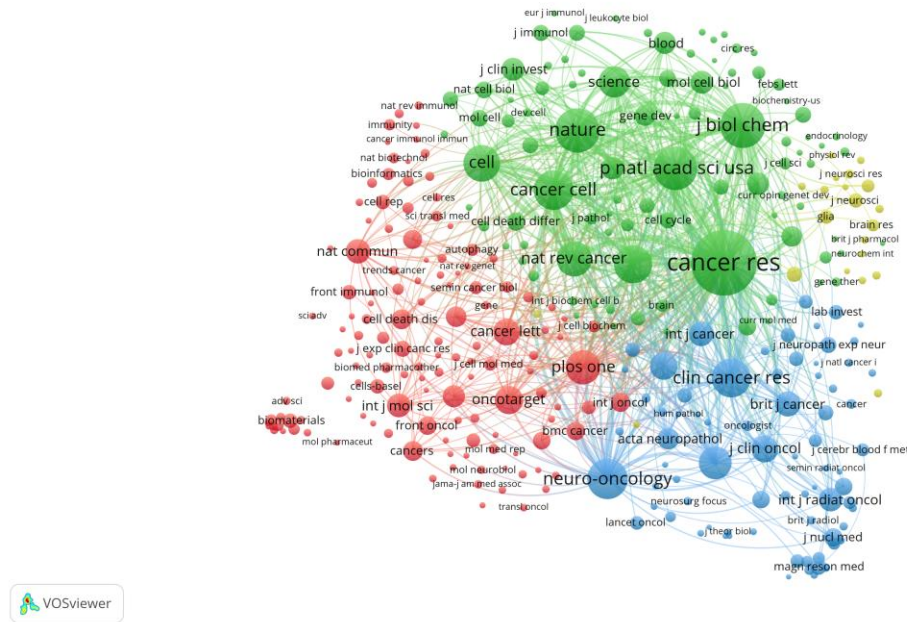


**Figure 6 Journal co-citation network visualization. Node size correlates with the journal's total citation frequency.**

The top 10 most prolific journals accounted for 393 articles (22.0% of the total dataset). Crucially, all these journals fall within the Q1 or Q2 quartiles of the JCR 2023 classification, confirming the high academic caliber of the published research. PLOS ONE emerged as the most productive journal with 53 publications, followed by ONCOTARGET (46 articles, Q1), NEURO-ONCOLOGY (44 articles, Q1), and INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES (41 articles, Q1), constituting the premier tier of publication volume. JOURNALS OF NEURO-ONCOLOGY, INTERNATIONAL JOURNAL OF ONCOLOGY, and CANCER RESEARCH also ranked within the top 10, forming a well-defined core publication matrix. Comprehensive analysis indicates that Cancer Research and Neuro-Oncology exert profound influence within the field. As a flagship oncology journal, Cancer Research maintains a robust impact factor (IF2023: 12.5) and international prestige. Literature published here traverses from fundamental mechanistic elucidations to advanced clinical applications. Neuro-Oncology (IF2023: 16.4), focusing exclusively on neuro-oncology, boasts deep specialized expertise, providing a critical platform for high-quality, translational glioma research. The journal co-citation network map (Figure 6), where node size mirrors total citation frequency and edge thickness reflects co-citation strength, clearly illustrates these dynamics. The premium cluster anchored by CANCER RESEARCH exhibits intense co-citation relationships with top-tier general science and oncology journals like Cell and Nature, collectively dictating the academic vanguard. Concurrently, the specialized cluster centered on NEURO-ONCOLOGY maintains a

tight professional dissemination network, while open-access platforms like PLOS ONE democratize the reach of scientific outcomes. Peripheral journals, though exerting less macroscopic influence, remain vital for disseminating niche discoveries or region-specific clinical data.

### 3.6 Cited Reference Analysis

The 1,983 core articles referenced a total of 63,817 citations. These cited references function as the architectural cornerstones of the field's theoretical framework, steering the evolutionary trajectory of future research. The top 10 milestone references aggregated 7,569 citations (Table 5),

| Top10 | Cited References                                                                                                                                         | Journal/year        | Citations |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------|
| 1     | Hypoxia-Inducible Factors Regulate Tumorigenic Capacity of Glioma Stem Cells                                                                             | CANCER CELL/2009    | 1107      |
| 2     | Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor                                                        | CANCER RES/2006     | 1084      |
| 3     | HIF-1 $\alpha$ regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment                                  | J EXP MED/2010      | 997       |
| 4     | Glioma-Derived Mutations in IDH1 Dominantly Inhibit IDH1 Catalytic Activity and Induce HIF-1 $\alpha$                                                    | SCIENCE/2009        | 982       |
| 5     | Glioma-Derived Mutations in IDH1 Dominantly Inhibit IDH1 Catalytic Activity and Induce HIF-1 $\alpha$                                                    | PROC NATL ACAD SCI  | 795       |
| 6     | Regulation of the HIF-1 $\alpha$ Level Is Essential for Hematopoietic Stem Cells                                                                         | CELL STEM CELL/2010 | 729       |
| 7     | The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis                                                                    | NEURO-ONCOLOGY/200  | 636       |
| 8     | The hypoxic microenvironment maintains glioblastoma stem cells and promotes reprogramming towards a cancer stem cell phenotype                           | CELL CYCLE/2009     | 621       |
| 9     | Extracellular vesicle-packaged HIF-1 $\alpha$ -stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells | NAT CELL BIOL/2019  | 618       |

**Table 5**The top ten most cited articles.

and the top 20 references exhibiting the most robust citation bursts are visualized in Figure 7.

## Top 20 References with the Strongest Citation Bursts

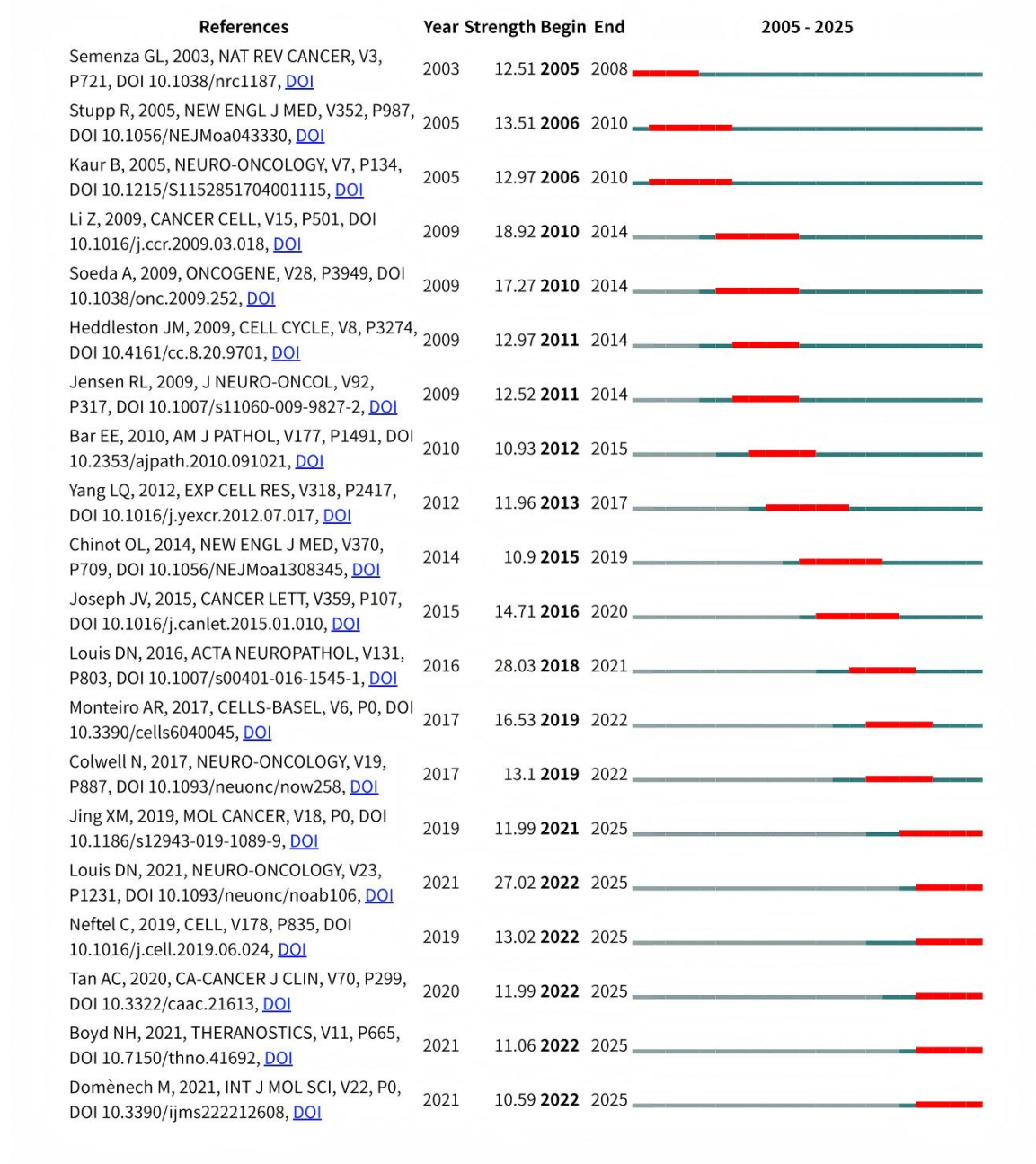


**Figure 7** Cite the top 20 most explosive references.

The top three most cited papers are universally recognized as foundational breakthroughs. The 2009 Cancer Cell article, "Hypoxia-Inducible Factors Regulate Tumorigenic Capacity of Glioma Stem Cells," ranked first with 1,107 citations. This study

systematically elucidated the indispensable regulatory role of HIFs in maintaining the tumorigenic potential of GSCs within the hypoxic niche, cementing the core theoretical scaffold for subsequent investigations. The 2006 Cancer Research article, "Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor," secured 1,084 citations by decoding the critical mechanisms through which GSCs drive neoangiogenesis via VEGF secretion, thereby proposing a novel target for anti-angiogenic intervention. The 2010 J Exp Med article, "HIF-1 $\alpha$  regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment" (997 citations), unraveled the HIF-1 $\alpha$ -mediated reprogramming of myeloid suppressor cells, directly bridging the hypoxic microenvironment with systemic tumor immunosuppression. Additional top 10 references addressed IDH1 mutation-mediated HIF-1 $\alpha$  regulation and hypoxia-driven GSC stemness maintenance. These landmark studies, predominantly published in premier journals between 2006 and 2010, constructed the foundational theoretical paradigm of glioma hypoxia research. Citation burst analysis, a powerful tool for detecting phase-specific hotspots, revealed that Louis DN's 2016 Acta Neuropathologica article—summarizing the WHO classification of CNS tumors—achieved the highest burst strength (28.03) during the 2018–2021 window. This paper served as the benchmark precipitating the shift toward molecular subtyping and precision diagnostics in neuro-oncology. Similarly, references by Li Z (2009) and Louis DN (2021) exhibited high-intensity bursts, vividly tracing the domain's evolutionary path from fundamental molecular exploration to precision clinical diagnostics, thereby illuminating the most promising avenues for future frontier breakthroughs.

### **3.7 Keyword Co-occurrence Analysis**

Keywords function as highly distilled condensations of a manuscript's core research themes. Keyword co-occurrence analysis is instrumental in uncovering semantic associations, identifying prevailing hotspots, and forecasting developmental trajectories. Utilizing CiteSpace, we generated a keyword co-occurrence visualization network for the

glioma and hypoxia domain (Figure 8).

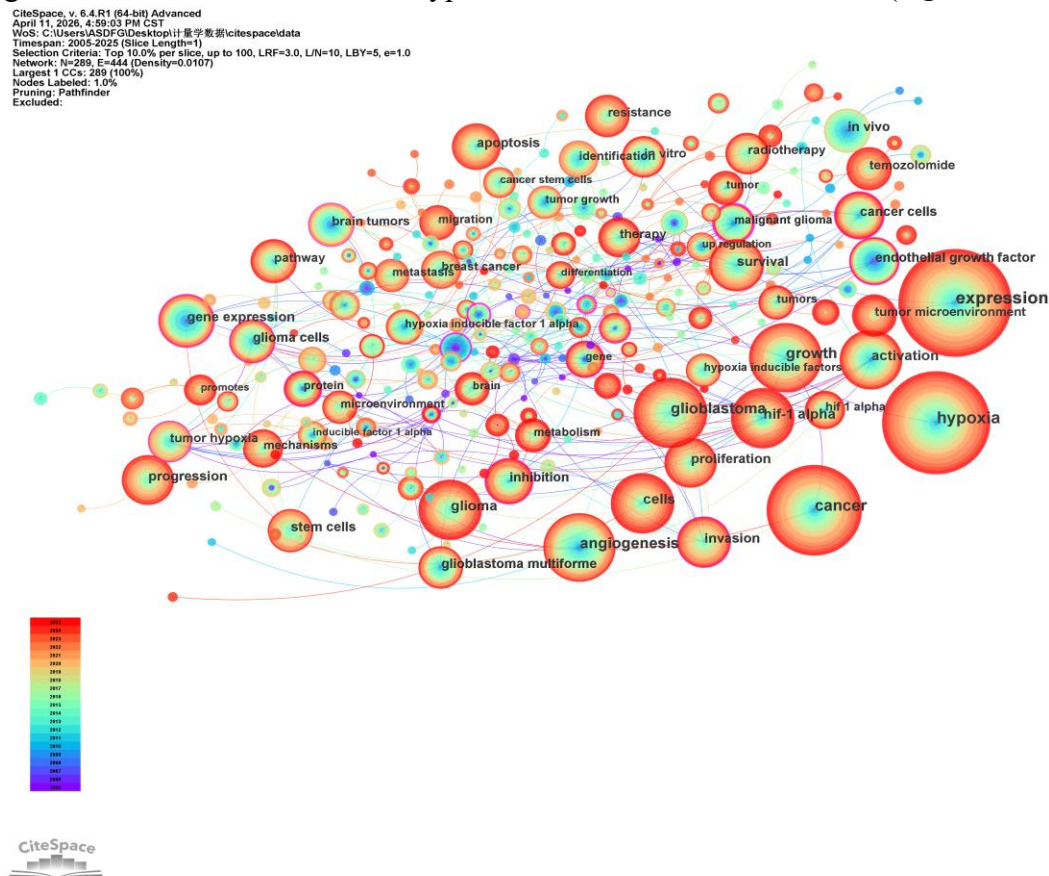


**Figure 8**Keyword co-occurrence visualization network.

The analysis identified "expression" (579 occurrences), "hypoxia" (532), "cancer" (400), "growth" (261), and "glioblastoma" (255) as the most frequent keywords. These terms delineate the central framework of the past two decades of research: the hypoxic microenvironment, glioma cell biology, and the malignant phenotype of glioblastoma. Cluster analysis of this network (Figure 9) generated 15 predominant thematic clusters, encompassing "hif-1 alpha" "cancer cells" "cancer stem cell" "tumor microenvironment"

"malignant glioma" and "migration."

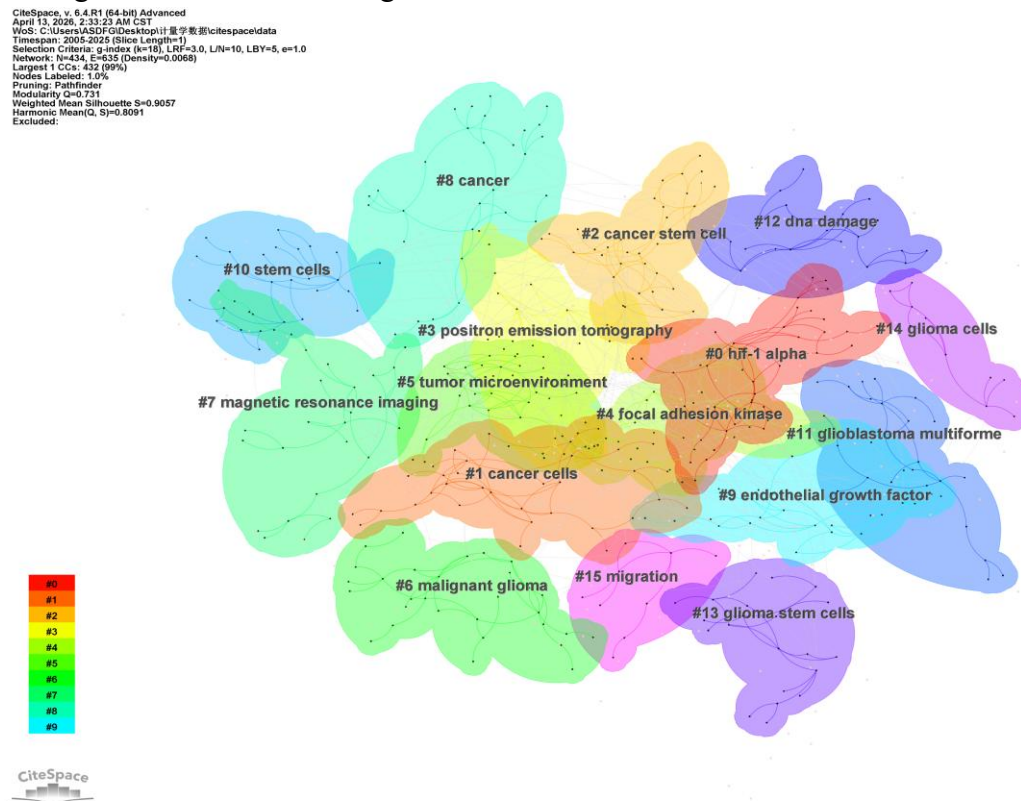
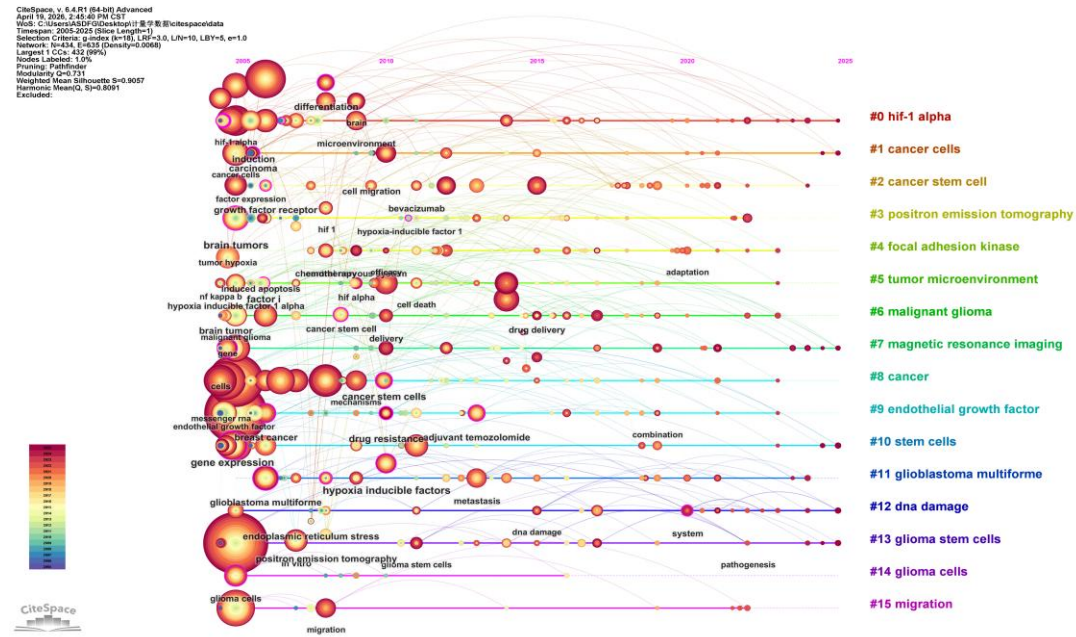


**Figure 9** Key word clustering.

Notably, clusters related to advanced imaging modalities, such as "positron emission tomography" and "magnetic resonance imaging," were also prominent. This comprehensive clustering spectrum completely captures the field's multidimensional scope—from sub-cellular mechanisms to clinical diagnostic technologies. Temporal dynamic features of these keywords were mapped via timeline visualizations (Figure 10)

and burst trend charts (Figure 11).



## Top 30 Keywords with the Strongest Citation Bursts

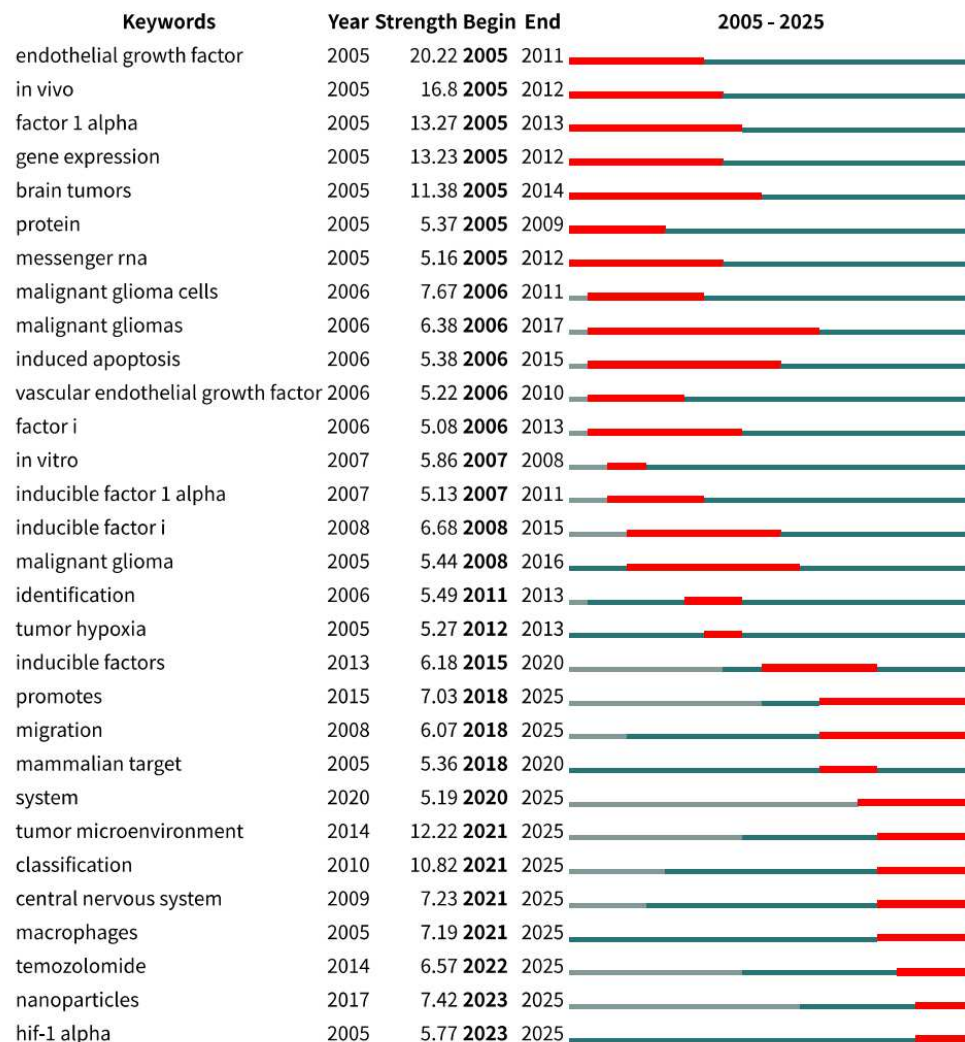


**Figure 11 Keywords with the strongest citation bursts and their temporal dynamics.**

The chronological evolution reflects both a continuity of legacy concepts and the rapid iteration of novel frontiers. Early investigations (2005–2011) were heavily concentrated on foundational molecular pathways, highlighted by bursts in "endothelial growth factor" (peak strength 20.22) and "gene expression." Conversely, over recent years (2021–2025), the focus has robustly pivoted toward complex systemic interactions, marked by powerful bursts in "tumor microenvironment," "macrophages" (representing tumor-infiltrating immune cells), and "nanoparticles." This clear trajectory signifies a profound paradigm shift from isolated, single-molecule pathway exploration toward holistic

microenvironmental remodeling and the translational application of smart nanomedicines, vividly charting the future roadmap of neuro-oncology.

## **4. Discussion**

Through an in-depth bibliometric analysis of 1,983 articles from the Web of Science Core Collection over a 20-year period (2005–2025), this study systematically delineates the evolutionary panorama of global glioma and hypoxia research for the first time. The results clearly indicate that the field has comprehensively transitioned from early "single HIF-1 $\alpha$  signaling pathway exploration" to a complex paradigm defined by "multi-omics microenvironmental networks". Particularly over the last decade (since 2016), catalyzed by the widespread adoption of single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and multi-omics integration technologies [52, 53], the research focus has experienced a significant shift. Investigations have expanded beyond traditional chemoresistance mechanisms into cutting-edge interdisciplinary areas, notably the tumor microenvironment (TME), metabolic reprogramming, and immune evasion [23, 26, 54]. This evolutionary model, propelled by iterative underlying technologies rather than isolated hypotheses, serves as the core engine behind the exponential explosion of literature, prompting the academic community to redefine the hypoxic microenvironment as a dynamic network system highly coupled across metabolic, immune, stromal, and neural dimensions [55, 56].

### **4.1 Deep Drivers and Paradigm Evolution of the Global Research Landscape**

Between 2005 and 2025, hypoxia-related glioma research progressed through a phase of basic accumulation and steady growth, entering a stage of high-level, accelerated development in 2017. The annual publication volume stabilized above 100 articles, with overall scientific interest continuously escalating. The global research architecture features dual-core leadership by China and the US, synergistic collaboration among multiple European nations, and rapid advancement by the Asia-Pacific region. Relying on mature scientific systems, high-end talent reserves, and original innovation capabilities, the US maintains a dominant lead in basic research directions, such as glioma stem cell-hypoxic niche interactions and core hypoxia signaling pathways. Its formidable citation metrics and hub position in international collaborations jointly reflect prominent academic leadership. China ranks first globally in both publication volume and highly cited scale, occupying 8 seats among the global top 10 institutions. Backed by massive clinical resources and continuous research investments, China has achieved leapfrog development in translational medicine, clinical validation, and targeted interventions. Cross-national and cross-institutional collaboration networks are becoming increasingly cohesive. Strategic collaborative clusters—primarily US-China, China-Germany, and US-Germany—have effectively dismantled resource barriers and driven the efficient

translation of basic research into clinical applications, serving as key dynamics for sustained innovation.

#### **4.1.1 Institutional Co-occurrence Characteristics and Global Collaboration**

##### **Network Landscape**

Institutional co-occurrence and network mapping identified 2,283 global research institutions actively participating in this field, with the top 10 entities generating 18.0% of the total output, forming a highly concentrated, elite research vanguard. The co-occurrence mapping elucidates that Chinese institutions comprise the most dominant output cluster, heavily represented by Soochow University, Shanghai Jiao Tong University, and Nanjing Medical University. This highlights the systematic strategic layout and robust, sustained productivity of domestic universities in neuro-oncological hypoxia research. Internationally, the University of Texas MD Anderson Cancer Center serves as a pivotal institution, exemplifying the benchmark standard for high-impact basic research and translational medicine through its exceptional citation frequencies. Concurrently, the German Cancer Consortium (DKTK) showcases the distinct, rigorous research strengths of European consortia. The global collaboration network is characterized by multi-centric hubs and tightly knit cross-regional connectivity. Top-tier domestic universities maintain high-frequency collaborative pipelines with leading cancer centers in the US and Germany. The synergistic integration between basic science institutes and high-volume clinical hospitals is remarkably prominent. This comprehensive "bench-to-bedside" integrated institutional model effectively bridges the gap from novel target discovery to robust clinical validation, providing the critical organizational framework required to drive tangible clinical outcomes in neuro-oncology.

#### **4.1.2 Academic Influence of Core Authors and Their Leading Role in the Field**

The foundational knowledge architecture and theoretical evolution of global glioma hypoxia research depend profoundly on the groundbreaking discoveries published by a select cohort of pioneering scholars in top-tier journals. These milestone papers form the topological nucleus of the entire citation network. The co-citation mapping unequivocally identifies Professor Semenza GL as the global leader, commanding 705 co-citations and a link strength of 9,780. As the pioneer of cellular oxygen-sensing mechanisms, his seminal discoveries regarding the transcriptional regulatory networks of HIFs—published in journals such as *Nature Reviews Cancer* and *Cell*—systematically decoded the genetic reprogramming of tumor cells under hypoxic stress [57-59]. This revolutionary finding not only deciphered the fundamental molecular cryptography of solid tumor progression but also equipped the neuro-oncology community with crucial targets to deconstruct the extreme stress-adaptive phenotypes intrinsic to glioblastoma (GBM).

Equally profound is the influence of Professor Stupp R in establishing clinical translational pathways. His landmark 2005 study published in *The New England Journal of Medicine* (the "Stupp protocol" establishing radiotherapy combined with

temozolomide) [60] ranks second globally with 391 high-frequency co-citations. This protocol completely rewrote the global standard of care for high-grade gliomas and formally integrated hypoxia-driven therapeutic resistance into the efficacy metrics of clinical trials, thereby serving as the ultimate reference coordinate for subsequent sensitizing drug development. Furthermore, the taxonomic revolution spearheaded by Professor Louis DN proved equally transformative. His comprehensive WHO CNS tumor classification summaries (achieving a staggering citation burst strength of 28.03) and revised typing criteria published in *Acta Neuropathologica* [61] formally enshrined molecular biomarkers as the gold standard in pathological diagnosis. This facilitated the deep integration of glioma spatial molecular heterogeneity with hypoxic phenotypic analysis, supplying the decisive taxonomic framework necessary for the transition from traditional histopathology to advanced spatial multi-dimensional networking.

In contrast, the expansive clusters of high-yield authors function primarily to advance these pioneering theories into systematic, large-scale validation and granular deep-dives. European scholars, exemplified by Steinbach JP, Ronellenfitsch MW, and Harter PN, frequently publish in *Cancer Research*, focusing on meticulous interrogations of microenvironmental stress adaptation and mitochondrial metabolic homeostasis. Conversely, Chinese scholars, represented by Li Gang, Xue Hao, and Guo Xiaofan, frequently publish in authoritative journals such as *Cancer Cell* and *Oncogene*. By fully capitalizing on extensive clinical cohort data, they have rapidly scaled investigations in highly competitive tracks, including hypoxia-mediated immune microenvironment remodeling, tumor-associated macrophage (TAM) polarization, and nanodelivery engineering. This intricate macroscopic collaborative web clearly reflects a tiered intellectual hierarchy and regional complementarity within the international scientific community: a select group of top-tier pioneers cemented the theoretical roots of oxygen sensing, standard-of-care therapies, and molecular classifications, while highly productive author clusters leverage efficient global collaborations to translate these foundational mechanisms into sophisticated systemic interventions and modern clinical practices.

#### **4.2 Core Research Focus: Systematic Radiation from Hypoxic Response to Subcellular Remodeling and Immune Evasion Networks**

Anchored upon the theoretical frameworks and clinical paradigms established by core pioneers, the focal points of global glioma hypoxia research have systematically radiated from basic mechanistic analyses toward sub-cellular reprogramming, immune evasion, and sophisticated multimodal interventions. Keyword clustering and citation burst analyses robustly validate this evolutionary trajectory.

#### **4.2.1 Spatiotemporal Heterogeneity and Heterogeneous Response Networks Driven by Oxygen Partial Pressure Gradients**

Rigorous analysis of keyword co-occurrence networks and time-zone mapping reveals that the cognitive paradigm of global glioma hypoxia research has completed a comprehensive transition from macroscopic histopathological phenotyping to microscopic, spatial, multidimensional network analysis [62]. In the field's infancy, academic efforts predominantly centered on the VEGF-driven pro-angiogenic cascades, anatomically mapped to microvascular proliferation surrounding pseudopalisading necrosis. Consequently, clinical translation was largely restricted to macroscopic anti-angiogenic blockades via agents like bevacizumab [63-67]. However, the global adoption of the WHO molecular biomarker subtyping criteria illuminated the severe limitations of purely targeting macroscopic angiogenesis, compelling a strategic pivot toward analyzing the spatiotemporally heterogeneous networks sculpted by oxygen partial pressure gradients [68]. The recent secondary explosive burst of HIF-1 $\alpha$  in knowledge graphs strongly corroborates this cognitive elevation: hypoxia is no longer viewed as a homogenous biochemical stressor [68]. Instead, it exerts highly precise, differential regulation mediated by distinct HIF family isoforms [69-71]. Specifically, HIF-1 $\alpha$  is acutely stabilized under severe hypoxic stress, rapidly transcriptionally upregulating critical glycolytic enzymes to dominate early-phase energy reconfiguration [72]. In contrast, HIF-2 $\alpha$  demonstrates superior physiological stability in chronic, persistent hypoxic niches, where it directly binds to the promoter regions of stemness factors to sustain the undifferentiated, resilient state of GSCs [42, 43, 73, 74]. This dynamic architecture, forged by heterogeneous microenvironments, not only dictates the spatial evolutionary trajectory of the tumor [68, 75] but also furnishes a novel molecular blueprint to decipher and overcome primary resistance to conventional single-target anti-angiogenic therapies.

#### **4.2.2 Subcellular Multi-Drug Resistance Networks Intertwined by Mitophagy and Epigenetic Lactylation**

The high spatial co-localization of keywords such as "drug resistance," "glioma stem cells," and "DNA damage" within the clustering networks forms a rigorous logical loop with temozolomide (TMZ) resistance on the temporal axis, indicating that the spatial heterogeneity of the hypoxic niche directly dictates the subcellular resistance phenotype [31, 68]. The pathophysiological coupling of DNA damage repair mechanisms and cell survival pathways correlates temporally with TMZ resistance, establishing CD133+ GSCs in the hypoxic core region as the fundamental cytological root of clinical chemoresistance [76]. To survive the destructive accumulation of reactive oxygen species (ROS) triggered by extreme hypoxia, tumor cells forcefully upregulate the outer mitochondrial membrane receptor NIX via HIF-1 $\alpha$ -dependent pathways [77], precisely orchestrating the autophagic degradation of damaged mitochondria (mitophagy) [78]. While eradicating the source of toxic ROS, this process concurrently provides carbon-

source support for GSCs under stress conditions through the recycling of degradation products [79-81]. Such subcellular survival adaptations have recently evolved into deeply intertwined, bidirectional metabolic-epigenetic interactive networks. Current evidence indicates that lactate mediates histone H3K9 lactylation, which subsequently upregulates the splicing factor LUC7L2. This induces MLH1 intron 7 retention, potentially inhibiting DNA mismatch repair via nonsense-mediated mRNA decay, thereby directly inducing TMZ resistance [82]. Concurrently, within the cytoplasmic post-translational modification dimension, lactate induces the specific lactylation of kinase NME1 at the K49 residue. This modification strongly activates NTP synthesis, providing an essential material foundation for stem cell DNA replication. Crucially, this dual-network operates entirely independently of classic MGMT repair mechanisms, yet it synergistically amplifies chemoresistance. These findings systematically decode the underlying molecular logic by which metabolic end-products architect formidable resistance barriers, thereby establishing highly promising clinical translational targets for deploying combination therapies with lactylation inhibitors to effectively reverse glioma resistance [67, 83].

#### **4.2.3 Tumor Immune Microenvironment Remodeled by Hypoxia and Blocking Pathways of Immune Cold Ecology**

The relentless accumulation and subsequent efflux of intrinsic metabolic byproducts from neoplastic cells ultimately catalyze a hostile, systemic remodeling of the external tumor immune microenvironment (TIME). This phenomenon has decisively propelled hypoxia research to the absolute vanguard of systemic host immune antagonism [51]. The recent, highly synchronized emergence of high-intensity keywords such as "tumor microenvironment" and "macrophages" distinctly marks the era where hypoxia research systematically deconstructs the TIME, profoundly elucidating the primary resistance mechanisms that define glioblastoma as an intractable "immune-cold" tumor. Operating as a pivotal initiating factor, hypoxia forces the extrusion of substantial lactate, drastically suppressing the microenvironmental pH to extreme acidic levels (5.9–6.8). This establishes an impenetrable physicochemical barrier that directly paralyzes the proliferation, activation, and infiltration of cytotoxic effector T cells. Concomitantly, tumor cells residing in the anoxic core secrete an abundance of exosomes laden with specific microRNAs. These exosomes function to remotely reprogram infiltrating myeloid cells, driving their robust polarization into pro-tumorigenic M2 macrophages (specifically, the Hypoxia-TAM subpopulation) [84]. Once polarized, these cells actively accelerate malignant tumor evolution through the copious secretion of characteristic cytokines and growth factors. Furthermore, they synergistically coordinate the profound upregulation of critical immune checkpoint molecules, notably PD-L1, effectively weaving a dense, highly suppressive immune-evasion network [85, 86]. The definitive elucidation of this systemic immune-evasion architecture forcefully highlights the urgent clinical necessity of modulating the TME to reinvigorate the host's anti-tumor immune

response [51]. Consequently, this has directly catalyzed the most advanced frontiers of translational medicine, particularly the implementation of multimodal, synergistic strategies leveraging state-of-the-art cellular engineering and innovative nanotechnology.

### **4.3 Outlook on Clinical Translation Challenges and Combination Therapy Strategies**

#### **4.3.1 Anatomical Barriers of the Nervous System and Translational Limitations of Intracranial Local Drug Delivery**

Despite unprecedented breakthroughs in fundamental research and advanced cellular therapies, the clinical translation of novel therapeutics for glioblastoma remains severely constrained by dual biological and engineering bottlenecks. While intelligent nanomaterials exhibit immense transformative potential for remodeling the microenvironment, the formidable physical barricades imposed by the blood-brain barrier (BBB) and blood-tumor barrier against macromolecules and engineered agents remain the central impediment to optimizing systemic delivery systems [87]. To completely circumvent these profound systemic delivery obstacles, cutting-edge CAR-T cell therapies specifically targeting CD133+ GSCs predominantly employ intracranial locoregional administration strategies [88-90]. However, the unavoidable emergence of severe safety liabilities—most notably neuroinflammatory storms, intractable cerebral edema, and critically elevated intracranial pressure—imposes exceedingly stringent constraints on clinical dosing schedules, frequency, and dose-escalation gradients [87, 91]. At the molecular target level, although hypoxia-driven metabolic reprogramming, epigenetic lactylation modifications, and precise deubiquitination regulation unveil entirely novel and highly attractive intervention sites [92, 93], the corresponding small-molecule inhibitors universally suffer from critical pharmacokinetic defects. These include notoriously poor druggability, inadequate in vivo structural stability, and exceptionally low central nervous system targeting specificity. Overcoming this profound biochemical impasse urgently necessitates the integration of next-generation targeted protein degradation technologies (e.g., PROTACs) to achieve a definitive, paradigm-shifting breakthrough in neuro-oncological therapeutics.

#### **4.3.2 Integration of Vascular Normalization and Armored Cell Therapy Bridged by Smart Nanomaterials**

The keyword clustering analytics vividly illustrate a major strategic transition, steering the global research focus definitively from isolated "target discovery" toward comprehensive "strategy integration". Pure single-agent immunotherapies, such as isolated PD-1/PD-L1 blockade, frequently fail in glioblastoma due to the intensely hypoxic and profoundly immunosuppressive microenvironment [94]. To decisively shatter this therapeutic impasse, future clinical breakthroughs will hinge upon the integration of smart nanomaterials, acting as sophisticated engineering bridges to facilitate the highly precise implementation of "multimodal and spatiotemporally

coordinated combined interventions" [87]. Traditionally, deploying anti-angiogenic agents (e.g., bevacizumab) to artificially induce vascular normalization only achieves a transient amelioration of microenvironmental hypoxia. Ultimately, the densely packed extracellular matrix and profound metabolic acidosis persist as stubborn, unyielding barriers that severely curtail the infiltration of cytotoxic immune cells [95]. State-of-the-art hypoxia/pH dual-responsive biomimetic nanocarriers provide a revolutionary solution by achieving the highly efficient, targeted co-delivery of ultra-low-dose vascular inhibitors, in situ oxygen-generating systems, and specific de-acidification media. This advanced nano-engineering not only dramatically prolongs and stabilizes the critical vascular normalization window but also actively blunts the severe biochemical toxicity inherent to the TME. Consequently, this successfully reprograms the hostile, immunosuppressive "immune-cold" tumor into an accessible, highly receptive "immune-hot" microenvironment tailored for robust T cell infiltration [96, 97]. Leveraging this optimized microenvironment, the subsequent sequential infusion of next-generation "armored" CD133-CAR-T cells—engineered to co-express vital cytokines like IL-7 and IL-15, or sophisticated anti-exhaustion molecules [90, 98]—can exponentially enhance both the penetration depth and the long-term killing persistence within deep intracranial solid tumors. This precisely eradicates the most resilient, highly resistant GSCs harboring within the anoxic core [99-101]. Furthermore, by synergistically integrating artificial intelligence-driven, multimodal radiomics [102-106] to non-invasively and dynamically map the spatiotemporal evolution of hypoxic gradients within the tumor [102, 103, 107], clinicians are provided with an unprecedented, real-time navigational compass for executing highly individualized, precision combination therapies. This multi-dimensional, heavily integrated strategy proves uniquely capable of systematically dismantling the microenvironmental foundation responsible for TMZ resistance and immune evasion, thereby representing one of the most exceptionally promising and high-impact clinical directions in contemporary neurosurgical cross-disciplinary translational research.

#### **4.3.3 Artificial Intelligence-Assisted Radiomics and Cross-Scale Multi-Omics Intelligent Navigation Systems**

The sophisticated keyword clustering map impeccably illustrates the ongoing, profound transition of clinical diagnosis and treatment from an archaic "experience-based subtyping" model to a highly precise, technologically advanced "data-intelligent navigation" paradigm. Compelled by severe practical realities and formidable clinical translation challenges—most notably the extreme difficulty of achieving effective blood-brain barrier penetration, the high-stakes safety risks inherently associated with local intracranial drug delivery, and the critically inadequate druggability of many targeted therapeutics—the field is actively advancing. The cross-scale, high-dimensional integration of AI-assisted multimodal radiomics alongside ultra-high-resolution spatial multi-omics is rapidly maturing into the ultimate, indispensable navigational tool

required for executing truly precise, individualized clinical interventions [106, 108]. Essential keyword clusters, specifically "positron emission tomography" and "magnetic resonance imaging," establish the foundational knowledge architecture essential for extracting complex, macroscopic imaging features. Through the deployment of highly advanced machine learning algorithms acting upon sophisticated quantitative PET and MRI sequences, researchers can now achieve non-invasive, dynamic, and extraordinarily precise mapping of both internal hypoxic gradients and the complex spatial distribution characteristics of elusive immunosuppressive cells residing deep within the tumor bulk [107, 109, 110]. By seamlessly fusing these macroscopic imaging phenotypes with microscopic single-cell transcriptomic sequencing and cutting-edge gene-editing technologies, investigators can successfully execute unparalleled cross-scale correlations. This allows them to directly link broad macroscopic imaging patterns with the highly specific, deeply complex microscopic heterogeneity of glioma stem cells and their unique, patient-specific resistant molecular profiles [109]. Ultimately, this highly advanced, intelligent navigation system provides absolutely critical, life-saving clinical support. It empowers surgeons to achieve the maximally safe resection of deeply embedded, hypoxic-resistant focal lesions during highly complex operative procedures. Furthermore, it affords clinicians the unparalleled ability to dynamically and precisely calibrate highly complex, multi-agent combination therapy strategies post-operatively, directly informed by real-time shifts in the tumor microenvironment [102]. Undeniably, this approach has rapidly ascended to become the preeminent, core research direction defining global glioma precision diagnosis and clinical translation. It furnishes the vital, indispensable technical reliance and highly promising translational prospects urgently needed to permanently shatter the formidable bottlenecks of hypoxia-driven treatment resistance, finally realizing the long-sought goal of highly individualized, meticulously stratified therapeutic interventions.

#### **4.4 Research Advantages and Limitations**

This study represents the inaugural, fully systematic bibliometric dissection of the glioma and hypoxia research domain. Its primary methodological advantage lies in the sophisticated integration of multidimensional visualization tools, enabling the precise, quantitative tracking of research paradigms migrating from simplistic "single pathway" models to the highly complex, tripartite "metabolism-immunity-stemness" network. However, inherent limitations associated with the primary data source (the WoS Core Collection) imply that select high-quality research outputs originating from non-native English regions may have been inadvertently excluded from the final analysis. Furthermore, the intrinsic, natural lag effect characterizing all bibliometric analyses suggests that the capture of comprehensive co-citation networks for ultra-cutting-edge, highly disruptive technologies emerging strictly between 2024 and 2025 (e.g., ultra-high-resolution spatial multi-omics and nascent CAR-T clinical trial data) may remain

partially insufficient. Nevertheless, this precise limitation robustly highlights highly critical, immediate directions for urgent, future literature tracking and systematic review.

## **5. Conclusion**

This study systematically and rigorously delineates the comprehensive developmental panorama of the global glioma hypoxia research field spanning the critical two decades from 2005 to 2025. Scientometric analyses unequivocally demonstrate that the field has aggressively advanced from the simplistic paradigms of isolated angiogenesis regulation into a highly sophisticated era defined by complex networks that seamlessly intertwine subcellular metabolic pathways, epigenetic modifications, and systemic immune microenvironments. Looking to the immediate future, breaking existing clinical translational bottlenecks in neuro-oncology will fundamentally depend on "med-eng crossover" strategies. Specifically, highly dynamic monitoring architectures reliant upon advanced AI-assisted multimodal radiomics, incredibly precise targeted interventions aimed directly at key epigenetic modifying enzymes, and the profound spatiotemporal remodeling of the hostile microenvironment via revolutionary nano- and cellular-engineering technologies will become absolutely paramount. Ultimately, this multi-dimensional integration strategy will systematically dismantle the microenvironmental foundation responsible for chemoresistance and immune evasion, offering critical forward-looking guidance essential for the ultimate conquest of glioma.

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## **Author Contributions**

HBL: Data curation, investigation, methodology, software, validation, writing—original draft, writing—review & editing. LY: Investigation, methodology, writing—review & editing. YNH: Formal analysis, resources, validation. GJY: Conceptualization, resources. WD: Resources. ZQG: Conceptualization, resources. BXL: Resources, writing—review & editing. XJS: Resources, writing—review & editing. SHM: Resources, writing—review & editing. JC: Resources, writing—review & editing. STL: Resources, writing—review & editing. LTM: Conceptualization, resources, writing—review & editing. YZ: Supervision, writing—review & editing. JS: Conceptualization, resources, writing—review & editing. HHH: Funding acquisition, conceptualization, supervision, resources, writing—review & editing.

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### **Data Availability Statement**

The bibliometric analyses were conducted using the Web of Science Core Collection database (Clarivate, <https://www.webofscience.com>). No additional web-based repositories or accession numbers are required. All search strategies and inclusion criteria are detailed in the Methods section.

### **Declarations**

#### **Ethics approval and consent to participate**

Not applicable. This study is a bibliometric analysis based on publicly available data from the WoSCC and does not involve human participants, animals, or identifiable personal data. Therefore, ethical approval and informed consent were not required. Clinical trial number: not applicable.

#### **Consent for Publication**

Not applicable.

#### **Competing Interests**

The authors declare no competing interests.

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