Transitioning from molecular methods to therapeutic methods: An in-depth analysis of glioblastoma (Review)

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Abstract. Glioblastoma (GBM) is the most aggressive primary brain tumour, characterised by high heterogeneity, aggressiveness and resistance to conventional therapies, leading to poor prognosis for patients. In recent years, with the rapid development of molecular biology and genomics technologies, significant progress has been made in understanding the molecular mechanisms of GBM. This has revealed a complex molecular network involving aberrant key signalling pathways, epigenetic alterations, interactions in the tumour microenvironment and regulation of non-coding RNAs. Based on these molecular features, novel therapeutic strategies such as targeted therapies, immunotherapy and gene therapy are rapidly evolving and hold promise for improving the outcome of GBM. This review systematically summarises the advances in molecular mechanisms and therapeutic approaches for GBM. It aims to provide new perspectives for the precise diagnosis and personalised treatment of GBM, and to ultimately improve the prognosis of patients.

Contents

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1. Introduction

GBM is the most common and lethal primary brain tumor in adults, characterized by a complex and diverse pathogenesis. In recent years, high-throughput sequencing technologies and multi-omics analyses have revealed intricate molecular features in GBM, including genetic mutations [such as epidermal growth factor receptor (EGFR) amplification, TP53 mutations and isocitrate dehydrogenase (IDH)1/2 mutations], epigenetic alterations (such as DNA methylation and histone modifications), the immunosuppressive nature of the tumor microenvironment and the regulatory roles of non-coding (nc) RNAs [such as circular (circ)RNAs and micro (mi)RNAs], as well as abnormal activation of multiple signaling pathways (such as the PI3K/AKT/mTOR and MAPK pathways) (1). These molecular changes not only drive tumor formation and progression but also influence the tumor's response to treatment.

Traditional GBM treatment strategies are primarily surgery-based. However, due to the highly invasive and diffuse nature of GBM, complete resection is often unachievable. Chemotherapeutic agents inhibit tumor growth by damaging tumor cell DNA, but many patients develop drug resistance, reducing therapeutic efficacy. In terms of targeted therapy, drugs targeting key molecules such as EGFR and vascular endothelial growth factor (VEGF) have been developed, but clinical outcomes remain unsatisfactory (2). Recent research has increasingly focused on immunotherapies, such as chimeric antigen receptor T-cell (CAR-T) therapy and checkpoint inhibitors, aiming to enhance the body's immune response to combat the tumor (3). In addition, gene therapy and physical therapies were shown to be potential applications. Despite significant progress in both basic research and clinical treatment for GBM, patient prognosis remains poor, highlighting the urgent need for further research to uncover more molecular mechanisms and develop more precise and effective treatment strategies. In the future, multidisciplinary

collaboration and personalized therapy may be crucial directions for improving GBM treatment outcomes. Therefore, a deeper understanding of GBM's molecular mechanisms and the development of novel therapeutic strategies have become key focuses of current research.

Literature selection. In the literature search for the present study titled 'Transitioning from molecular methods to therapeutic methods: An in-depth analysis of glioblastoma', to enhance transparency, the selection of references adhered to strict inclusion and exclusion criteria. The search was conducted in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) and the search terms were as follows: 'Glioblastoma', 'molecular mechanisms' and 'treatment'.

The literature inclusion and exclusion criteria were as follows: i) Selection of studies directly related to the transition of GBM from molecular mechanisms to therapeutic approaches to ensure the relevance of the research topic; ii) Selection of papers published in authoritative peer-reviewed academic journals to ensure the credibility and scientific rigor of the studies; iii) Rigorous research methodology, reliable data, clear study design, and reasonable data analysis; iv) Recent publications to reflect the field's (of which 68% are published in the last five years). (68% of which are references from the last five years).

By specifying and strictly adhering to these inclusion and exclusion criteria, the high quality, relevance, and reliability of the selected references were ensured, thus providing a solid foundation for the study and enhancing the scientific validity of our manuscript.

2. Comprehensive overview of GBM

Essential clinical characteristics and diagnostic directions for GBM. Globally, GBM stands as the leading invasive primary malignant brain tumor, accounting for ~15% of intracranial and 45 to 50% of primary malignant brain tumors (4). The primary clinical signs of GBM are primarily linked to the tumor's substantial impact on the brain's nearby activities, including symptoms such as headaches, epilepsy, changes in emotions or personality, speech modifications, diminished sense of touch, hearing and smelling abilities, and compromised physical coordination and balance (5).

Traditional methods for identifying GBM require histopathological analysis, using the observation or non-recognition of pathological features such as microvascular expansion and necrosis as benchmarks. In 2021, The World Health Organization (WHO) updated its Classification of Central Nervous System Tumors, 5th Edition (CNS5) system, revising the diagnostic criteria for GBM (6): The diagnostic requirements for GBM are based on the absence of isocitrate dehydrogenase and histone 3 mutations as cornerstones, and the IDH mutation category has been eliminated.. While various low-grade (WHO grade 2 or 3) diffuse astrocytomas do not have these histological features, their clinical presentations also reflect those of GBM. As a result, in 2021, the WHO's categorization brought forth new molecular benchmarks: Simultaneous amplification of the entire chromosome 7 and the eradication of the full chromosome 10 (+ 5/10); mutations in the telomerase reverse transcriptase (TERT) promoter; and the enhancement of the EGFR. The aforementioned mutations in WHO grade 2 or 3 tumors could upgrade them to the level of WHO grade 4 (molecular GBM) (4).

Details regarding epidemiology and risk elements. Epidemiological data indicate that the global yearly incidence of GBM is ~3-4 cases per 100,000 individuals. Each year, the US sees an approximate GBM occurrence of 3.19 in every 100,000 individuals (7). As age progresses, the incidence of GBM significantly increases, mainly among the 45 to 70 age bracket, with men having higher frequencies than women, exhibiting a gender ratio of ~1.6:1 (8). The prognosis for GBM is dismal, with a median survival duration of 12-15 months following diagnosis, and a 5-year survival rate close to 5% (9).

The development of GBM is linked to a range of genetic and environmental factors. The presence of a familial lineage, coupled with distinct genetic changes, significantly increases the likelihood of developing the disease. A close link exists between genetic conditions such as neurofibromatosis type 1 (NF1) and Li-Fraumeni syndrome and the development of GBM (10). In addition, changes in genes such as TP53, phosphatase and tensin homolog (PTEN) and EGFR are more commonly observed in patients with GBM (11). Considering diverse environmental factors, elevated concentrations of ionizing radiation are recognized as a critical risk element for GBM, while elements such as mobile phone use and exposure to electromagnetic fields lack a direct connection to GBM (12). Investigations focusing on grasping the epidemiological characteristics and risk facets of GBM are vital for understanding its evolution and devising effective prevention and treatment strategies. Future studies should explore more profoundly the exact part that genetics and environmental factors play in the development of GBM, offering new viewpoints for the prevention and therapy of this malignant neoplasm (Fig. 1).

3. Molecular mechanisms

Process of molecular typing in GBM. According to the molecular characteristics of GBM, researchers have classified it into the following subtypes: The classical type is represented by EGFR amplification, TP53 mutation and PTEN deletion; the neural type has cellular characteristics similar to normal nerve cells and shows high levels of neurodevelopment at the molecular level; the mesenchymal type possesses higher stem cell characteristics and proliferation ability, often accompanied by NF1 mutation and upregulated expression of immune-related genes; and the primary type is more frequently seen in young patients, along with IDH1 mutation and TP53 mutation (13).

Alterations in genetics and epigenetic studies. Studies reveal that various vital genetic alterations in GBM, including TP53, IDH1/2 and EGFR, have a significant impact on the development, progression and treatment of tumors (1).

Changes in TP53 are considered to be among the prevalent mutations found in GBM. P53, the protein encoded by the TP53 gene and known for tumor suppression, acts as a stimulant for the cell cycle and apoptosis, with its reduced function leading to rampant cell proliferation and tumor development (14). Approximately 80% of GBM cases show mutations in TP53 (15).

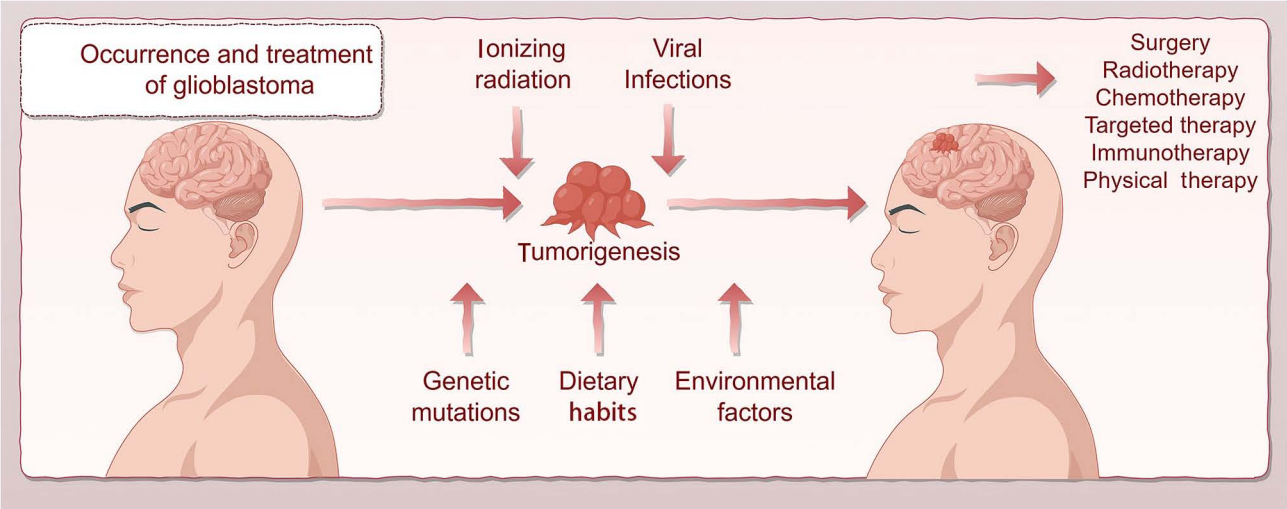

Figure 1. Representation of the risk factors and treatment strategies for GBM (generated with Figdraw).

IDH is the chief source of nicotinamide adenine dinucleotide phosphate in the cytosol of brain cells, where its variants, the cytoplasmic IDH1 and mitochondrial IDH2, reduce DNA damage and lipid oxidation (16). Despite the WHO CNS5 having discontinued IDH as a conclusive sign of GBM, changes in the IDH1 and IDH2 genes are equally influential in triggering GBM (17). Cancerous growths carrying IDH mutations demonstrate a prolonged survival period, unlike those in IDH-wild-type tumors that lack IDH mutations (18). The proteins IDH1 and IDH2 function to convert isocitric acid into α-ketoglutarate (AG). When altered, AG transforms into 2-hydroxyglutarate, an essential metabolite of the gliomagenogenesis process (19), triggering changes in epigenetics and the onset of tumors.

The EGFR is part of the receptor tyrosine kinase (RTK) category, which includes four specific receptors [human EGFR (HER)1-4/ErbB1-4]. This factor is crucial for maintaining cellular existence, proliferation, migration and averting cell demise, intricately connected to pathways such as PI3K/AKT, rat sarcoma (RAS)/MAPK/ERK, phospholipase C (PLC)/protein kinase C (PKC) and JAK/STAT (2). Changes and increased expression of the EGFR gene are frequently found in GBM (20), accounting for ~40% of all primary GBM cases (11).

These modifications result in an uneven rise in receptor activity, promoting tumor cell growth and longevity, aiding in tumor blood vessel formation and reducing the effectiveness of chemotherapy and radiotherapy for GBM (2).

PTEN, located on chromosome 10q23.31, is a tumor suppressor gene encoding a phosphatase protein. PTEN plays a vital role in regulating cellular growth, multiplication and survival processes, and is significantly involved in the molecular evolution of gliomas (21). Xia *et al* (22) found that eliminating or modifying the PTEN gene activates the PI3K/AKT pathway continuously, leading to the activation of mTOR and suppression of glycogen synthase kinase (GSK)-3β, thereby increasing the movement and infiltration of GBM cells (23). In addition, alterations or decreases in PTEN expression levels are linked to increased severity of disease, less positive results and lower overall survival rates (21). Apart from genetic modifications, key genetic alterations, including DNA methylation, histone changes and other epigenetic shifts governed by ncRNA, play a crucial role in shaping GBM (24).

DNA methylation is a frequent alteration found in epigenetic sequences. Typically, methylation processes occur in CpG Islands, which impact the gene's role in transcription. The state of methylation in the O6-methylguanine-DNA methyltransferase (MGMT) promoter of GBM is linked to the effectiveness of alkylation chemotherapy in patients with GBM, acting as a vital measure for both prognosis and the success of the treatment.

DNA methylation represents a prevalent epigenetic modification, predominantly occurring at CpG islands within gene promoter regions, thereby exerting regulatory control over gene transcription. In GBM, the methylation status of the MGMT gene promoter has been established as a critical biomarker, demonstrating a significant association with the therapeutic response to alkylating agents and serving as an independent prognostic factor for patient outcomes (25). Modifying the methylation of the MGMT promoter initiates gene suppression, leading to reduced DNA repair capability and higher sensitivity of tumor cells to chemotherapy. In addition, methylation at the promoter region of key tumor-inhibiting genes such as retinoblastoma (Rb)1, cyclin-dependent kinase inhibitor A and PTEN is observed in GBM, highlighting their vital contribution to tumor growth (26).

Changes in histones, crucial to epigenetic activities such as acetylation and phosphorylation, significantly influence gene expression by influencing chromatin architecture (27). Frequently, the erratic functions of histone deacetylase (HDAC) and DNA methyltransferase have been noted in instances of GBM (28). The ability of HDAC inhibitors to stop GBM cell proliferation and induce cell death suggests their potential application in the treatment of GBM (29).

Lately, ncRNAs have garnered substantial attention as essential regulators. NcRNAs include a set of RNA entities lacking proteins, notably miRNAs, long ncRNAs (lncRNAs) and circRNAs (30). NcRNAs play a pivotal role in regulating gene activity, fostering cellular development, triggering apoptosis and forming the surrounding microenvironment of

tumors (31). Furthermore, it is a key factor in the epigenetic regulation of GBM (32).

MiRNAs are types of small RNA molecules of ~22 nucleotides in length, which serve to either inhibit translation or assist in its degradation through attachment to specific gene mRNAs. Within GBM, alterations in the expression levels of specific miRNAs influence the growth and spread of tumors (33). For instance, miR-21, which is upregulated in GBM, has the ability to suppress the expression of genes such as PTEN and p53, thereby boosting cell proliferation, survival, proliferation and infiltration (34). Furthermore, miRNAs such as miR-10b, which is upregulated in GBM cells, contribute to the incursion and proliferation of these cancerous cells (35). Tan *et al* (36) uncovered that modifications in miRNA levels impact the biological functions of GBM cells, proposing new therapeutic ideas.

LncRNAs, a category exceeding 200 nucleotides in length, play a critical role in regulating gene expression and cellular functions. In GBM, a notable expression pattern of lncRNAs is intimately associated with the evolution and progression of tumors (37). LncRNAs affect gene expression through their interaction with transcription factors and enzymes that modify chromatin structures. In GBM, LncRNAH19 demonstrates considerable levels of expression, contributing to the growth of tumor cells by inhibiting the function of tumor suppressor genes (38). LncRNAs contribute to tumor avoidance in immune responses by altering immune cells' functions in their immediate environments, and lncRNAMALAT1 aids in tumor avoidance by changing T-cell functions (39). In addition, lncRNAs such as HOTAIR aid in modifying H3K27me3 by interacting with the polycomb repressive complex 2, causing a reduction in chromatin and gene suppression, which in turn affects the proliferation and locomotion of GBM cells (40).

CircRNA is a special type of ncRNA that forms a circular structure through head-to-tail ligation. This circular structure endows circRNA with higher stability and specificity. It has been demonstrated that the levels of oncogenic circRNAs are elevated in GBM samples (41), thereby promoting GBM proliferation, invasion, glycolysis and epithelial-mesenchymal transition (EMT) (42). In addition, circRNAs can influence the transcription process by interacting with transcription factors, thereby regulating the biological behaviors of tumor cells (43).

Apart from DNA methylation, histone modifications and ncRNA alterations, other epigenetic phenomena such as chromatin alteration and RNA shifts play a crucial role in the processes of GBM. Changes and anomalies in chromatin remodeling structures, such as the SWI/SNF complex, often arise in GBM, with these structures governing gene expression by altering nucleosome locations and chromatin structure (44). Modifications in RNA, such as the N6-methyladenosine change, are found in GBM, affecting tumor-specific gene expression via effects on RNA balance, translation efficiency and splicing processes (45).

The emergence and development of GBM originate from a blend of numerous genetic mutations and epigenetic shifts. Alterations in genetics and epigenetics provide insight into the molecular dynamics of GBM and pave the way for creating alternative diagnostic and treatment strategies. Further studies should thoroughly investigate the exact mechanisms of these mutations and alterations to strengthen the basis for tailored GBM therapies.

Paths of signal transmission. RTKs, a type of transmembrane receptor protein, form part of an extracellular structure linking with specific ligands such as EGF, platelet-derived growth factor (PDGF), VEGF, fibroblast growth factor (FGF) and hepatocyte growth factor, while their intracellular part shows activity in tyrosine kinase. When ligands bind to RTKs, they initiate either dimerization or multimerization, subsequently activating their tyrosine kinase activities. Upon activation, RTKs begin the autophosphorylation process, phosphorylating tyrosine residues and acting as docking sites to draw in and activate different downstream signaling proteins.

Pathway involving PI3K/AKT/mTOR. Phosphorylation of tyrosine components initiates RTKs, which activate the PI3K/AKT/mTOR pathway, vital for the proliferation, endurance, motility and metabolic processing of GBM cells. An alarming 86% of individuals with GBM exhibit genetic alterations in their RTK/PI3K pathway (46).

Upon activation of a cell surface receptor (e.g., growth factor receptor or insulin receptor), PI3K is recruited to the membrane via its regulatory subunit, and its catalytic subunit (p110) subsequently phosphorylates the substrate PIP2 (phosphatidylinositol-4,5-bisphosphate) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 acts as a second messenger and specifically binds to the PH domain of AKT to recruit AKT to the cell membrane. PIP3 acts as a second messenger and specifically binds to the PH domain of AKT to recruit AKT to the cell membrane. Activated AKT regulates key biological processes such as cell proliferation, survival, metabolism and apoptosis by phosphorylating downstream effector molecules, mTOR and GSK3β (47).

MDM2, subsequently targeted by AKT, advances to the nucleus post-AKT phosphorylation, attaching to p53 with the objective of dismantling tumor suppressor genes, resulting in changes to MDM2, noted in 87% of GBM patients (14). The activation of AKT promotes the cell cycle by phosphorylating and inhibiting the inhibitors p27 and p21. This action leads to the stabilization and proliferation of cyclin D1/D3 (48).

A vital molecule in the PI3K/AKT signaling pathway, mTOR, is divided into two separate complexes: mTORC1 and mTORC2. Such complexes boost cellular growth, fat generation and nucleotide generation by phosphorylating and inhibiting lipin-1 in nutrient-rich and growth factor-rich settings. Furthermore, mTORC1 acts to activate hypoxia-inducible factor 1α (HIF-1α). Furthermore, mTORC1 enhances the mitochondrial tetrahydrofolate cycle's metabolic rate, particularly in the purine synthesis pathway, by boosting the amounts of active transcription factor 4 and methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase (49).

mTORC2's phosphorylation and activation of AKT trigger overlapping positive feedback loops in the PI3K route, indicating a possible critical function in GBM's resistance against PI3K/AKT/mTOR suppression. mTORC2's evolving roles encompass regulating glycolysis driven by AKT and MYC, managing lipid processing and regulating glutamine metabolism within GBM. By contrast, mTORC2 plays a crucial role in regulating the longevity of cells and restructuring the cytoskeleton, thus enhancing the migration and penetration of GBM cells (50).

Distinct from PI3K/AKT signaling, the EGFRvIII-facilitated mTORC2 mechanism initiates phosphorylation and inhibits the class IIa HDAC complex, leading to the deacetylation of forkhead box (FOX)O transcription factors. Inhibiting FOXO activity leads to heightened MYC levels, decreased gluconeogenesis and improved glycolysis (51). Therefore, the RTK/PI3K/AKT/mTOR mechanism impacts diverse functions, including governing the cell cycle, metabolic activities, cellular expansion and various epigenetic regulatory roles.

Ras/Raf/MEK/ERK. The MAPK/ERK pathway begins at the cellular RTKs stage (52). Once the receptor is activated, RAS proteins detect signals via the growth factor receptor-bound protein 2/SOS complex. RAS triggers RAF kinase family proteins, such as BRAF, through their attachment to GTP. After activation, RAF persistently phosphorylates and MAPK/ERK kinase (MEK), which then triggers ERK phosphorylation, prompting its migration to the nucleus and activation of multiple transcription factors and their respective effector molecules (53).

Aberrant activation of the MAPK/ERK signaling pathway in GBM is closely associated with a variety of molecular events (54), Dysregulation of this pathway is usually driven by overactivation or mutation of upstream receptor tyrosine kinases (RTKs, such as EGFR) (e.g., EGFRvIII), oncogenic mutations in RAS or RAF genes, resulting in sustained phosphorylation of ERK proteins. Upon translocation into the nucleus, activated ERK promotes cell cycle progression (e.g., up-regulation of Cyclin D1, CDK4), cell growth and proliferation through the regulation of key transcription factors (e.g., c-Myc, CREB, AP-1, etc.), as well as inhibits the expression of pro-apoptotic genes (e.g., BAX, PUMA) and proteins. In addition MAPK/ERK signaling prolongs tumor cell survival and enhances drug resistance by activating anti-apoptotic pathways (e.g. BCL-2 family proteins) and telomerase activity, ultimately leading to malignant progression of GBM (55). Within the Raf protein family, BRAF stands out as the main factor contributing to cancer development. In BRAF, the class I point mutation known as BRAFV600E is recognized as the primary mutation. The mutation in question, unique among BRAF mutations in GBM, is found in a small number but appears predominantly in children, young adults and epithelioid GBM. Changes in BRAF trigger its inherent activation, resulting in extended stimulation of its ensuing effectors MAPK, MEK1/2 and ERK1/2. Furthermore, ERK and AKT/mTOR collaboratively focus on proteins like MYC and HIF1α, collectively providing cancer cells with the essential proteins and energy for their development and vigorous proliferation.

Furthermore, the MAPK/ERK pathway enhances the movement and aggressive capability of GBM cells by altering the extracellular matrix (ECM) and the cytoskeleton's structure (56). Activating ERK augments the generation of matrix metalloproteinases (MMPs), resulting in the collapse of ECM components and the promotion of tumor cell spread. Furthermore, the MAPK/ERK pathway is instrumental in angiogenesis, regulating VEGF levels, helping establish new blood vessels in tumors and providing GBM cells with sufficient nourishment and oxygen (57).

PLC-γ is a member of the PLC family, encompassing 13 separate subtypes. Typically, this is activated by RTK or G protein-coupled receptor, particularly post-RTK activation, through phosphorylation at Y sites (tyrosine residues), which in turn activates PLC-γ. The PLC-γ enzyme plays a role in decomposing phosphatidylinositol 4,5-bisphosphate (PIP2), leading to the formation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 latches onto IP3 receptors on the endoplasmic reticulum, producing calcium ions (Ca^{2+}) and subsequently increasing cellular calcium ion concentrations. DAG interacts with PKC, consequently activating PKC (serine/threonine protein kinase). Upon activation, PKC can phosphorylate various downstream proteins, including transcription factors, kinases and structural proteins, thereby controlling biological functions such as cellular growth, survival, mobility and apoptosis (58).

In GBM, it is frequently observed that mutations or the overproduction of RTKs such as EGFR are prevalent (59). The erratic activation of such RTKs governs cytoskeletal remodeling via the phosphorylation of associated proteins, such as actin-binding proteins, facilitating the movement and penetration of GBM. PKCα aids in the expansion and maintenance of glioma cells through the EGFR/mTORC pathway. Under hypoxic conditions, PKCβ activation promotes tumor angiogenesis by enhancing the migratory and proliferative capacity of brain endothelial cells. Therefore, PKCβ may contribute to the uneven vascular formation observed in GBM development, highlighting its significance in therapy (60). Although the PI3K and MAPK pathways are separate drivers of the evolution and progression of GBM, PKC pathways cross these paths, uncovering a complex web of signals within GBM cells.

Furthermore, PKC is capable of regulating MMP activities and VEGF expression, allowing tumor cells to penetrate the neighboring matrix, infiltrate adjacent tissues and enhance the development of tumor blood vessels, thus providing essential nutrients and oxygen for tumor growth (61).

Mechanism involving NF-κB signalling. NF-κB, a type of transcription factor, is made up of heterodimers formed by five elements within the family: p50, p52, RelA, RelB and c-Rel. Activation usually takes place when surface receptors such as TNF-α receptor 1 or IL-1 receptor are stimulated (62). Triggering NF-κB promotes tumor growth and proliferation, hinders programmed cell death and increases treatment tolerance (63).

NF-κB's extensive cancer-causing effects include regulating gene transcription to avert cell death, boosting cyclins to fast-track the cell cycle and initiating the synthesis of proteins associated with cellular invasion and angiogenesis, such as MMP and VEGF. Changes in the NF-κB gene's genetics, dysfunctions or disruptions in the mechanisms governing NF-κB dimer activation can lead to various forms of cancer. Regarding GBM, there is a regular occurrence of erratic activation of NF-κB, with several processes associated with diminished NF-κB signaling in gliomas (64). In the context of GBM, both EGFR and PDGFR display inconsistent functions, and the pathways triggering cancer through EGFR and PDGFR play a key role in the growth and penetration of tumor cells. Furthermore, the reduction of PTEN and NF1 is linked to atypical NF-κB activity in GBM, leading to increased PI3K activity. The lack of Krueppel-like factor 6, known for inhibiting NF-κB, triggers its activation in GBM (65).

Wnt pathway. The influence of the Wnt signaling pathway is crucial in shaping essential cell operations throughout the development stages of the central nervous system. A strongly

established connection exists between the overactivation of Wnt receptors and the promotion of harmful alterations, resulting in the development of brain tumors (66).

GBM displays heightened activity in its Wnt pathway (67). It is recognized that the unconventional WNT5A molecule enhances neuronal cell differentiation and plays a substantial role in cellular multiplication. Knockdown of WNT5A in GBM cells using short hairpin RNA (shRNA) significantly reduced their proliferation rate, suggesting a pro-tumorigenic role for WNT5A. By contrast, activation of the uncommon WNT signaling pathway is closely connected to the aggressive characteristics of GBM cells. The existence of atypical elements such as WNT5A and frizzled class receptor 2 has a significant impact on cell penetration in GBM, markedly affecting the outlook (68). In addition, a variety of minimally present cell adhesion substances (such as cadherins and connectors) hinder the adhesion of tumor cells, thereby affecting the Wnt/β-catenin pathway, notably by enhancing the role of β-catenin, thus bolstering the tumor's propensity to penetrate (69).

Minor surroundings of tumors. GBM represents the gravest onset of brain cancer, exhibiting a significant variation among and within the tumors, a limited lymphocyte count and a plethora of myeloid subgroups in both malignant and non-malignant ventricular regions, resulting in an environment primarily conducive to tumor growth and immune suppression (70). In contrast to conventional ECM, the GBM ECM is enriched with hyaluronic acid, collagen, glycoprotein-1, neuroglycan (NG), chondroitin sulfate proteoglycan 4 (CSPG4/NG2), versican, and tenascin-C, collectively fostering tumor invasion and therapy resistance (71). In addition, numerous GBM cells infiltrate adjacent brain layers, modifying the neural environment to promote neuron electrochemical interactions and the metabolic connection with benign astrocytes, thereby encouraging growth (72).

Within the GBM ECM, tumor growth, including microglia, neutrophils, dendritic cells, bone marrow and myeloid suppressor cells, constitutes 50% of total tumor growths (73). Neutrophils, myeloid-derived suppressor cells and bone marrow-derived macrophages in this category are associated with negative outcomes, decreased survival rates and a higher chance of recurrence in GBM (74). Tumor-associated macrophages (TAMs) play a pivotal role in shaping the immune-suppressing environment during GBM's pathological stages. TAMs are primarily categorized into two types: Conventional macrophages (M1 type) and those activated through different pathways (M2 type). In the GBM context, TAMs often exhibit the M2 phenotype, which is recognized for boosting tumor cell growth, invasion and the creation of new blood vessels, while also inhibiting immune responses that combat cancer.

TAMs regulate the immunosuppressive state of the tumor microenvironment by discharging a range of cytokines and chemokines, such as IL-10, TGF-β and VEGF (75). These components obstruct the function of effector T cells and promote the accumulation of regulatory T cells, thus exacerbating the immunosuppressive environment. In addition, TAMs display a complex interaction with GBM cells. Within GBM cells, increased concentrations of colony-stimulating factor (CSF)-1 and C-C motif chemokine ligand (CCL)2 boost TAM attraction and polarization, and the dissemination through CSF-1R and CCR2 elevates the survival and efficacy of TAMs. Cytokines improve the intrusion and mobility of tumor cells and bolster their toughness, thus intensifying the progression of GBM (76). Deterioration of the blood-brain barrier (BBB), mainly due to inflammation and pressure from tumors, and the formation of new blood vessels, largely attributed to significant VEGF, leads to increased GBM blood flow. The presence of hypoxia and macrophages plays a role in harming the BBB by fostering immune suppression via the CCL4-CCR5 axis and the invasion by GBM (77). Recently, there has been a notable escalation in attention towards therapies targeting TAMs within the immunosuppressive microenvironment (78).

Comprehending angiogenesis via the VEGF signaling process. The distinctive characteristic separating GBM is its widespread vascularization (79). Inside the vicinity of a tumor, cancer cells promote development, mobility and the formation of new blood vessel networks by releasing various pro-angiogenic substances that meet the demand for oxygen and vitamins, providing pathways for the spread of cancer cells. A considerable quantity of VEGF predominantly gets activated by oxygen scarcity and a variety of cytokines in the area encircling the tumor. In environments with insufficient oxygen, the activation of VEGF gene transcription by HIF-1α results in a rise in VEGF expression levels. Tumor cells, macrophages and nearby cells in the microenvironment also release VEGF and other elements that facilitate the process of angiogenesis. Research suggests that GBM cells are high in VEGF production, triggering the following PI3K/AKT and Ras/MAPK pathways when receptors attach (80). This process enhances endothelial cell proliferation and migration, facilitates ECM remodeling, and promotes cell-cell adhesion, ultimately driving the formation and maturation of new blood vessels. VEGF, through its autocrine and paracrine mechanisms, provides tumors with essential blood and nutrients, enhancing the tumor cells' resilience and invasive capacities to create a complex network that benefits the tumor. Furthermore, VEGF increases the permeability of blood vessels, leading to swelling adjacent to the tumor and greatly affecting its growth and spread (Fig. 2).

Apart from its reliance on the creation of endothelial cell blood vessels, GBM also demonstrates a behavior known as vasculogenic mimicry (81). This relates to cancer cells creating formations similar to blood vessels, separate from endothelial cells. Cancer cells, by creating a microcirculation network, aid in blood flow, particularly in cases of restricted angiogenesis, thereby meeting the tumor's dietary needs. The progression of tumors heavily relies on this procedure.

Bevacizumab, an antibody targeting VEGF, impedes the process of angiogenesis by counteracting VEGF and hindering its adherence to VEGFR (82). Studies in medical environments suggest that bevacizumab may partly slow down the development of GBM and improve patient survival. However, the treatment targeting VEGF faces significant obstacles, particularly regarding resistance to treatment and the adjustment of the tumor. Tumor cells can combat anti-VEGF therapies by boosting other angiogenic components (such as basic FGF) or activating alternative pathways like Ang-2 signaling.

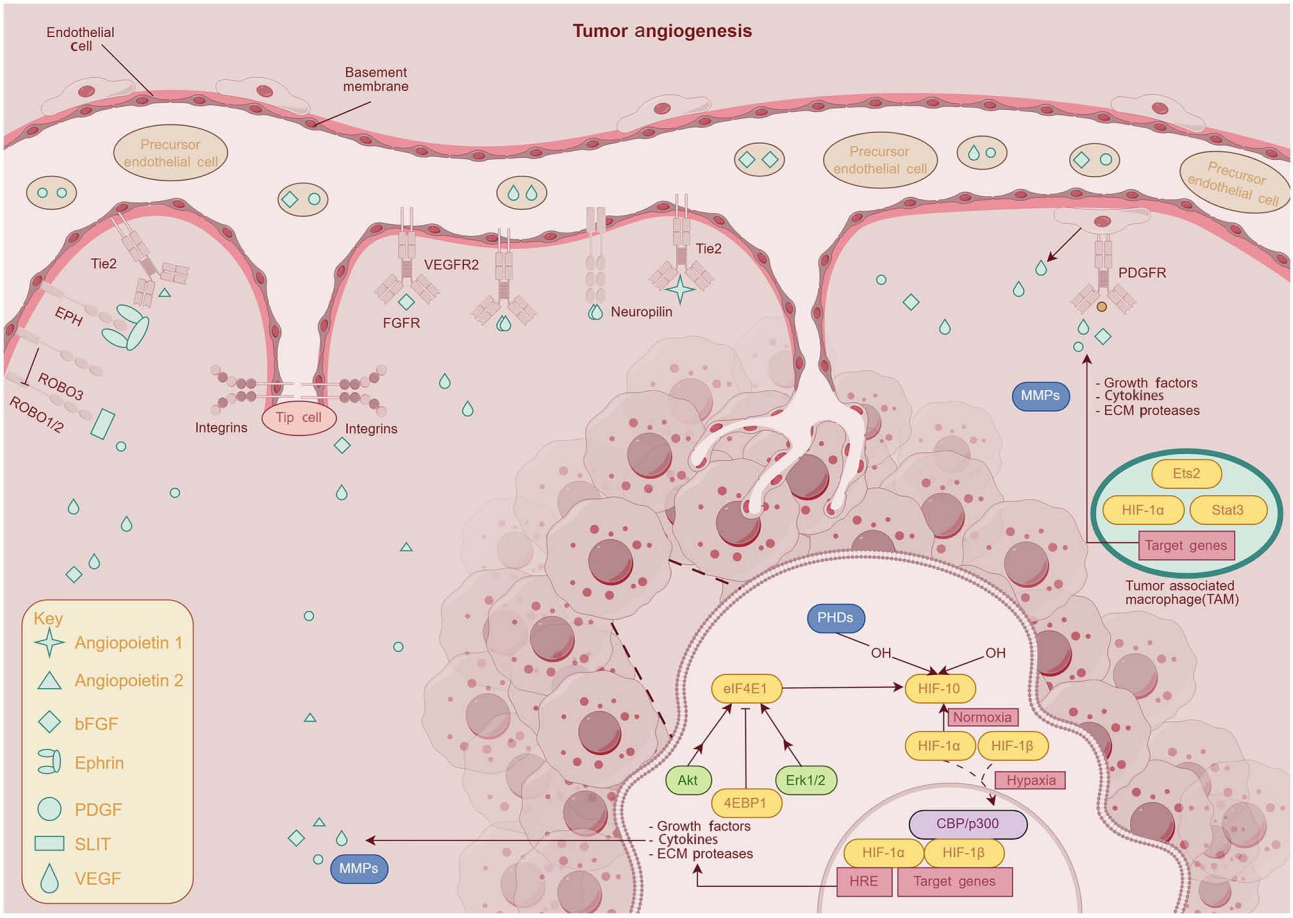

Figure 2. Schematic depicting the angiogenesis of tumors (generated with Figdraw) Tie2, Tie2 receptor tyrosine kinase; EPH, erythropoietin-producing hepatocellular receptor; ROBO, roundabout guidance receptor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor, PHDs, prolyl hydroxylase domain proteins ; eIF4E, eukaryotic initiation factor 4E, Akt, protein kinase B; Erk1/2, extracellular signal-regulated kinase 1/2, 4EBP1, eukaryotic translation initiation factor 4e-binding protein 1; MMPs, matrix metalloproteinases; FGFR, fibroblast growth factor receptor, VEGFR2, vascular endothelial growth factor receptor 2; HIF, hypoxia-inducible factor; HRE, hypoxia response element; PDGFR, platelet-derived growth factor receptors; Ets2, endothelial transcription factor 2.

Dynamic interplay between stromal cells and GBM. In GBM, the complex dynamics between stromal tissue and tumor growth markedly affect how tumors evolve, develop and resist treatments. Stromal cells include a range of cells such as fibroblasts, endothelial and smooth muscle cells, and immune cells like macrophages and lymphocytes, to name a few. These cells interact with GBM cells through several techniques, encompassing direct cellular communication, expulsion of signaling molecules and reorganization of the ECM. Cancer-associated fibroblasts (CAFs) amplify tumor cell growth, infiltration and transit by disseminating different growth signals and cytokines, including TGF-β, MMPs and FGFs (83). Furthermore, CAFs encourage tumor propagation by altering the ECM and rearranging the stroma structure. Endothelial cells facilitate tumor growth and spread by discharging substances like nitric oxide and prostaglandins and by regulating blood flow in the vicinity and stimulating stromal cells. Apart from the earlier referenced cell types, astrocytes augment the development and mobility of GBM cells by secreting various neurotrophic components and cytokines, such as glial cell-derived neurotrophic factor and CXCL12 (84). By contrast, oligodendrocytes influence the growth and maturation stages of GBM cells through direct engagement (85).

Tumor stem cells

Markers within GBM stem cells (GSCs). GSCs, a subpopulation of undifferentiated cells within GBM, are characterized by their dual capacity for self-renewal and multilineage differentiation into heterogeneous tumor cells. GSCs drive tumor initiation, progression, recurrence, and resistance to therapy by serving as a persistent reservoir of therapy-resistant cells (86). Morphologically, GSCs typically appear as diminutive, compact cell masses, marked by sparse cytoplasm, widespread nuclei, evenly dispersed nuclear chromatin and separate nucleoli. GSCs demonstrate a notable capacity for enduring and adaptable differentiation abilities, in addition to their strong aggressive nature and resistance to medication. Understanding the role of GSCs in GBM is vital for devising effective treatment strategies (Table I).

Role of stem cells in tumor occurrence and development. GSCs are acknowledged as the essential cells responsible for the onset of GBM. These components maintain tumor growth and variety through their self-regeneration and conversion into various cell types. Ishii *et al* (87) effectively separated a group of GBM cells with stem cell properties, proficient in forming neurospheres *in vitro* and triggering highly invasive tumors in living organisms. Further research has shown that GSCs can

Table I. GSCs markers and their functions.

Surface markers of GSCs	Molecular type	Function	Detection method	(Refs.)
CD133	Membrane protein	Stem cells maintain and self-renew	Flow cytometry, immunohistochemistry	(159)
Sox2	Transcription factor	Maintain pluripotency and self-renewal	qPCR, immunohistochemistry	(160)
OLIG2	Transcription factor	Promote the differentiation of glial cells	Western blot, immunohistochemistry	(161)
CD44	Mucin glycoprotein	Cell-cell and cell-matrix interactions	Flow cytometry, immunohistochemistry	(162)
A2B5	Ganglioside	Glial precursor markers	Flow cytometry, immunohistochemistry	(163)
ALDH1A3	Enzyme	Metabolic regulation, self-renewal	Flow cytometry, qPCR	(164)
L1CAM	Mucin glycoprotein	Cell migration and invasion	Flow cytometry, immunohistochemistry	(165)
Nestin	Fibroin	Neural stem cell markers, involved in cytoskeleton remodeling	Western blot, immunohistochemistry	(166)

qPCR, quantitative PCR; GSCs, glioblastoma stem cells.

maintain their stem cells and self-reproduction functions by triggering numerous signaling pathways, such as Notch, Wnt and Sonic hedgehog. In these pathways, the role of the Notch signaling pathway is pivotal for the self-replacement and endurance of GSCs. Ryskalin *et al* (88) found that obstructing the Notch signaling pathway significantly reduces GSCs' capacity for self-regeneration and potential to develop tumors.

GSCs have an increased capacity for mobility and penetration, aiding their expansion in brain tissues and the formation of new tumor sites. Research suggests that GSCs aid in tumor angiogenesis and matrix reconstruction by discharging various MMPs and VEGF, interacting with different cells in the tumor's surrounding environment to accelerate tumor development (89).

Furthermore, GSCs display a pronounced ability to form blood vessels. Releasing Notch1 signaling units via exosomes improves the multiplication of nearby cells and blood vessel generation, altering the development of tumors and the outcomes of treatments (90). Although therapies like surgery, radiation therapy and chemotherapy may momentarily shrink tumors, GSCs demonstrate significant resistance and extended viability. The cells demonstrate immunity to apoptosis, a result of both radiotherapy and chemotherapy, by enabling multiple anti-apoptotic pathways, including PI3K/Akt and Bcl-2. Furthermore, they enhance drug resistance through the production of varied drug outflow proteins such as ATP binding cassette subfamily G member 2 and multidrug resistance 1, reducing the accumulation of chemotherapy drugs in cells, which may lead to tumor recurrence (91).

4. Pathological mechanisms

Characteristics of organizational pathology. A hallmark of GBM is its cellular heterogeneity, characterized by diverse morphologies, dysregulated signaling pathways (92). Nuclei display considerable pleomorphic traits, differing in dimensions and shapes, and show an uneven distribution of chromatin, often leading to hyperchromatic and multinucleated instances. Within GBM, mitotic figures are common, indicating a significant rate of cell proliferation. In addition, the occurrence of large and multinucleated giant cells is evident, underscoring the vast variety found within cancer cells (93).

GBM is primarily characterized by microvascular development and areas of necrosis (94). Under the microscope, tumor tissues often exhibit microvascular proliferation, marked by enlarged capillary walls and clusters of endothelial cells, termed 'glomeruloid bodies'. Tumor arteries, recently formed, provide a plentiful blood source, aiding the rapid proliferation and spread of tumor cells (95). Tumorous areas of the tissue frequently exhibit necrotic features, typically appearing as unevenly shaped zones encircled by cancer cells in a way that mimics pseudopalisading, leading to the unique 'pseudopalisading necrosis' state. The formation of necrotic areas is closely connected to localized oxygen deficiency and poor nutrient supply, a consequence of the tumor's rapid expansion.

Glial fibrillary acidic protein (GFAP), a specific marker protein indicative of astrocytes, is profusely present in GBM (96). Immunohistochemical analysis shows inconsistent amounts of GFAP in GBM cells, with certain areas exhibiting GFAP-positive cancer cells while others have fewer. The variety noted may be associated with different stages of differentiation and the functional attributes of cancer cells. However, tumor cells devoid of GFAP typically show increased mitotic activity and invasive ability, suggesting a heightened likelihood of being malignant.

Besides GFAP, other markers such as microtubule-associated protein 2 (MAP2) and neuron-specific enolase (NSE) in

neurons and glia have also been observed in GBM cells (97). The expression of these indicators further reveals the multifaceted potential and variety inherent in GBM neurons. Primarily existing in neuronal cells, MAP2 is also observed in certain GBM cells, suggesting a high probability of these cells to display features akin to neuron differentiation. NSE may serve as an additional neural marker, with its expression in GBM representing the multifaceted nature and variety of the cancerous cells.

Typically, GBM tumors exhibit significant swelling. Swelling arises due to cancer cells releasing active vascular and permeability-enhancing substances. Peritumoral edema exacerbates a patient's neurological issues and additionally assists in the spread and penetration of cancer cells. GBM cells possess the capability to secrete various cytokines and enzymes, such as MMPs and VEGF. These components disrupt the BBB, increase the permeability of blood vessels and promote the emergence of a tumor microenvironment (98).

GBM cell biological activity. GBM represents a gravely malignant tumor located within the central nervous system. Rapid proliferation, a lack of tolerance and the aggressive behavior of this organism play major roles in the obstacles encountered in its therapeutic approach.

The amplification and alteration of the EGFR gene in GBM often result in the growth of cancer cells by enhancing the PI3K/AKT signaling pathway downstream, thus increasing the dependence on growth signals. GBM cells exhibit a significant ability to resist cellular demise, primarily attributed to the modification and reduced function of the p53 gene. In GBM cells, deactivating the function of p53 leads to the suppression of apoptotic pathways, thus improving the survival rates of the tumor cells. Furthermore, in the context of GBM, activating the NF-κB signaling route is vital for combating apoptosis.

Triggering the PI3K/AKT pathway promotes the creation of GBM by reducing cell death, accelerating the cell cycle, enhancing tumor cell multiplication and facilitating metastasis (99). In addition, the athanogene 3 (BAG3), associated with Bcl2, belongs to the BAG family. Under low-oxygen circumstances, there is an observed increase in tumor cells' production of the BAG3 protein, similar to the reaction to HIF-1α. A study showed that lower BAG3 expression leads to decreased HIF-1α in both normoxic and hypoxic states, causing a pause in GBM growth and a rise in apoptosis (100). The CD2-associated protein (CD2AP) acts as an adaptable protein structure, overseeing cell adhesion and diverse modes of communication. Zhang *et al* (101) found that CD2AP improves the onset of GBM by activating tripartite motif containing 5-driven NF-κB signals.

MMPs, a group of zinc-dependent endopeptidases, play a crucial role in the progression of GBM (102). Commonly, GBM displays an increased presence of subtypes like MMP-2, MMP-9 and MMP-14 (103). MMPs possess the ability to decompose various components of the ECM, including collagen, laminin and fibronectin, among others. The impairment of the ECM interferes with the robust structure of normal tissue, permitting the movement and infiltration of cancerous cells. For instance, MMP-9 can break down type IV collagen, essential for the basement membrane, allowing tumor cells to penetrate the vessel walls and enter the bloodstream, consequently increasing the likelihood of metastasis. The expression and activity of MMPs are governed by various signals that exist inside and outside the cell. Factors like hypoxia, inflammatory cytokines (TNF-α, IL-1β) and growth components (including EGF, PDGF) can trigger GBM cells to release a higher quantity of MMPs.

EMT refers to a biological process in which epithelial cells transform deliberately to become cells that display mesenchymal traits. During this stage, cancer cells lose their adhesion ability, their epithelial polarity vanishes, and their invasion and migration potential is eventually enhanced. Principal characteristics include reduced synthesis of cell adhesion agents (such as E-cadherin), the transformation of the cytoskeleton from a cytokeratin-focused to a vimentin-focused form, and the structural qualities of mesenchymal cells. The activation of EMT is driven by starting elements, a range of transcription factor families and several signals transmitted via channels such as TGF-β/Smad and Wnt/β-catenin, along with related genes, all contributing to the incursion and progression of glioma (104).

Concentrating on the invasive processes of GBM requires altering the cytoskeleton, relocating cells and dismantling the extracellular matrix (105). Elements within the Rho GTPase family, namely ras homolog family member A (RhoA), Rac family small GTPase 1 and cell division cycle (CDC)42, are crucial for managing cytoskeletal restructuring processes (106). The serine/threonine kinases Rho-associated coiled-coil containing protein kinase 1 (ROCK1) and ROCK2 are essential downstream components of RhoA, influencing mechanisms such as cell invasion, proliferation and muscle contraction (107). Upon activation of RhoA, its interaction with downstream effector proteins (e.g., ROCK) enhances contraction of the intracellular actin-myosin cytoskeleton. This contraction remodels cellular morphology and generates mechanical forces that promote tumor cell motility (e.g., migration and invasion).. Studies reveal that the teneurin transmembrane protein 1 (TENM1) aids in altering the cytoskeleton and parenchymal invasion in GBM cells by triggering the RhoA-ROCK pathway (108).

CDC42, part of the Rho GTPase group, functions as a trigger within cells. The element under study shows elevated levels in various human cancerous formations and plays a crucial role in the advancement of tumor growth (109). Upon activation, CDC42 initiates actin polymerization, resulting in filopodia that help cells locate their external surroundings and choose migration points. Elevated CDC42 levels are associated with an unfavorable prognosis for patients with glioma and boost CDC42-induced cell death in tumors by blocking the p21 (RAC1) activated kinase/AKT/MDM2/p53 pathway in these cells (110).

The PI3K/AKT pathway is vital for cellular infiltration and mobility in GBM (111). Activation of PI3K leads to the production of PIP3, which then activates AKT. The mechanism inhibits GSK-3β, prompting β-catenin accumulation and nuclear entry, subsequently activating genes associated with cellular proliferation and movement.

The function of focal adhesion kinase (FAK) is essential for signal transmission in the interaction between cells and the ECM (97). The attachment of the ECM to integrins activates FAK, sparking a series of signal transmissions through phosphorylation and interactions with other molecules such

as Src family kinases and PI3K, thereby regulating cellular adherence, locomotion and penetration.

5. Existing treatment methods

The surgical removal of an exceptionally cancerous first-generation brain tumor can significantly reduce the tumor's severity, decrease its symptoms and prolong life expectancy (112). However, the unclear boundaries of a tumor may result in residual tumor cells after surgery, prompting their reemergence and leading to adverse outcomes such as infections, bleeding and nerve damage. The importance of these risks escalates if the tumor is located in a brain area that is responsive to activity (113).

The considerable advantages of radiation therapy originate from its unobtrusive character. The technique efficiently eliminates minor lesions left after tumor removal, and with diagnostic imaging like MRI, radiation is limited to a certain location (114). The most effective approach for individuals under 70 years of age or those who are generally healthy is starting radiation treatment between 4 to 6 weeks post-surgery or before, in combination with chemotherapy. Radiotherapy has the potential to change the tumor's surrounding environment, alter the functioning of immune cells and enhance the immune system's capacity to detect and direct tumors. However, owing to either inherent or tumor environment resistance to radiation, tumor recurrence remains inevitable (115).

The efficacy of chemotherapy lies in the immediate damage to tumor cell DNA, leading to either their death or the cessation of cellular proliferation. Currently, just three chemotherapy drugs have been granted authorization by the US Food and Drug Administration (FDA). The initial categorization includes nitrosourea medications such as carmustine and lomustine; however, their usage is typically halted in treatments due to liver and kidney toxicity (116). Temozolomide (TMZ) is second approved, standing as the only chemotherapy drug sanctioned by the FDA for primary GBM treatment. TMZ swiftly penetrates the BBB and modifies tumor cell DNA through methylation, inflicting damage on DNA, hindering mismatch repair, obstructing DNA replication and inducing apoptosis in rapidly dividing cells (117).

A substantial blockage of the BBB hinders the penetration of various medications into the nervous system. This characteristic obstructs the distribution of chemotherapy drugs to cancer cells, leading to a decrease in the drug's quantity and a decline in treatment efficacy (118). Given the significant variation both within and across tumors, a variety of tumor cell clusters respond variedly to identical drugs, thus bypassing the effects of chemotherapy (119). GSCs mainly neutralize drug damage through the amplification of anti-apoptotic proteins, initiating drug expulsion processes (such as P-glycoprotein), along with other tactics (120). Within GBM tumors, the surrounding environment markedly dampens the immune defense, as cancer cells defy typical chemotherapy using the expulsion of immunosuppressive components and manifestation of immune checkpoints such as programmed cell death ligand 1 (PD-L1), among other ways (121). In the end, the Warburg effect assists cancer cells in enduring conditions of limited oxygen and nutrients, and metabolic increase can bolster drug resistance by regulating cell signaling routes (119).

6. Emerging treatment strategies

In recent years, treatments such as surgery, radiotherapy and chemotherapy have provided certain benefits, but they have not significantly increased the overall survival duration (9). The rise of molecular biology, innovative therapeutic techniques and cutting-edge platforms has catalyzed significant shifts in the methods for treating GBM. Advancements in fields such as immunological checkpoint inhibitors, cancer virus therapies, adoptive cell healing, nanoparticles, convection-enhanced delivery, and boron neutron capture therapy have fueled optimism for tackling GBM (122).

Targeted therapy. Creating targeted therapies for GBM has gained research interest due to its unique characteristics and negligible adverse effects. EGFR and VEGF are key players in various malignancies, GBM included, and are central to therapeutic efforts (2). EGFR inhibitors uniquely bind with EGFR, thereby halting its ensuing signaling routes, which consequently curtail the expansion and multiplication of cancer cells. Compounds blocking EGFR, such as gefitinib and erlotinib, have shown varying effectiveness, notably in patients with EGFRvIII-mutant GBM. However, the diverse nature of tumors and complex EGFR signaling mechanisms limit the efficacy of EGFR inhibitors, which may result in resistance (2).

VEGF plays a crucial role in creating blood vessels and shaping the tumor-surrounding environment in GBM (123). By using anti-VEGF agents to block the binding of VEGF to its receptors, the growth and function of tumor vasculature can be inhibited, thereby restricting the blood supply to the tumor. The human-originated anti-VEGF monoclonal antibody Bevacizumab has shown success in recurrent GBM management in various clinical trials, thus extending the duration of patient survival. However, the persistent efficiency and safety of VEGF inhibitors demand further research and exploration.

Gene therapy and gene editing technologies. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology, famed for its significant gene editing power, has drastically altered the disciplines of genetics and molecular biology (124). This technique precisely modifies specific genes in cancer cells, providing novel possibilities for GBM treatment (125).

CRISPR screening has been used in multiple steps of studying GBM progression, including tumor initiation, tumor growth and tumor invasion. To uncover the genetic factors regulating GBM tumor initiation, Chow *et al* (126) developed an adeno-associated virus (AAV)-mediated *in vivo* CRISPR screening approach.

They injected an AAV library targeting common mutations in human cancers' tumor suppressor genes into the brains of mice conditionally expressing Cas9 in astrocytes. Using this method, they identified different mutation spectra in tumors and driver combinations concurrently occurring in GBM, such as beta-2-microglobulin, neurofibromin 1 and zinc finger CCCH-type containing 13-retinoblastoma 1. Targeting key oncogenes or tumor suppressor genes, such as TP53 and EGFR, inhibits tumor cell growth, proliferation and invasion.

CRISPR screening has also been used to study other aspects of GBM progression. Tu *et al* (127) used CRISPR screening to identify the genetic vulnerability of TERT promoter mutations (TPMs) in GBM, a genomic alteration present in >80% of GBM cases. While TPM status is associated with differential gene expression and dependence on ETS transcription factors such as E74-like ETS transcription factor 1, ETS variant transcription factor 4 and GA binding protein transcription factor, it is not particularly related to TERT dependency. Lin *et al* (128) employed an *in vivo* and *in vitro* CRISPR-Cas9 screening strategy to discover that ubiquitin ligase RB binding protein 6, ubiquitin ligase promotes GSC proliferation, self-renewal and tumor growth by regulating variable polyadenylation through ubiquitination.

Immunotherapy. Immunotherapy aims to activate or fortify a patient's immune defenses to identify and eliminate tumor cells. Currently, immunotherapy leads the forefront in cancer treatments, attracting attention through numerous methods including immune checkpoint inhibitors, antibody-based therapies, cellular therapies, cytokines, cancer vaccines, oncolytic viruses, and more, with a special emphasis on therapies like mesenchymal stem cells (MSCs) and adoptive cell transfer (ACT) (129).

MSCs are a type of adult stem cells designed for self-renewal and varying lineage diversification, typically found in regions such as the bone marrow, fat tissue and the umbilical cord. Primarily, MSCs are intended for GBM treatment due to their unique attraction to tumors and their capacity to alter immune reactions. A study revealed that MSCs protect from rapid degradation of medicinal substances through their response to chemical components present in the tumor milieu, reducing widespread side effects and enhancing treatment success by precisely aiming at cancerous tissues for drug administration (130).

By genetically altering MSCs, the distribution of anti-cancer medications or genes to GBM lesions can enhance treatment success and reduce extensive toxic responses. Additionally, MSCs are crucial in regulating immunity, holding the ability to curb inflammation and manage immune cells through the release of various cytokines and growth factors. This type of immunological adjustment intensifies the tumor's microenvironment, strengthens immune responses to tumors and suppresses the spread of tumors (131).

ACT is as a laboratory-based treatment approach, boosting the immune cells in patients or donors and then reintroducing them into the patient for an improved immune response against cancer. During the treatment of GBM, research primarily focuses on CAR-T, tumor-infiltrating lymphocytes (TILs) and cytokine-triggered killer cells (CIKs).

CAR-T cell therapy involves genetically modifying T cells in a patient through gene engineering, leading to the production of CARs that detect tumor antigens, thereby enhancing the T cells' ability to kill cancer. CAR-T is notably effective in preventing blood cancers (3). For the treatment of solid tumors, CAR-T cells targeting certain antigens like EGFRvIII and IL13Rα2 have been developed to fight GBM, proving successful through early and advanced clinical trials. However, the vast variety in GBM and the tumor's internal environment, which hinder immune reactions, remain the key barriers in CAR-T cell therapy (132).

Utilizing TILs for treatment involves isolating infiltrating lymphocytes from the patient's tumor, amplifying and activating them externally to the body, and then reinserting them into the patient to enhance the immune response. Using TILs as a treatment has been shown to be effective in addressing solid cancers, such as melanoma. Immune CIK cells, known for their wide-ranging tumor-destroying capabilities, attain anti-cancer effects through the release of various cytokines. Although immunotherapy was proven to be effective in GBM treatment, its lasting effects and safety remain unconfirmed by comprehensive clinical studies (133).

The role of programmed cell death protein 1 (PD-1) in tandem with PD-L1, a binding agent, plays a crucial role in evading detection by the tumor's immune defense (134). Blocking PD-1/PD-L1 revitalizes tumor T-cell activities by hindering their interaction, demonstrating efficacy in treating a range of cancers such as melanoma, non-small cell lung cancer and bladder cancer (135).

In the case of GBM, the extent of PD-1/PD-L1 expression is closely connected to the immune system of the tumor. Preliminary clinical tests have shown promising results for PD-1 inhibitors such as pembrolizumab and nivolumab in managing GBM, demonstrating prolonged impacts in several instances (136). However, the success of PD-1/PD-L1 inhibitors in managing GBM depends on various factors, such as the tumor's environment and patient genetics, highlighting the need for further biomarker studies to adjust patient decisions (137).

Nanometer drugs and drug delivery systems. Nanoparticles show great potential in the field of drug delivery due to their unique physicochemical properties (138). By loading cytokines into nanoparticles, the pharmacokinetics (e.g., extended half-life), pharmacodynamics (e.g., targeted delivery), and overall therapeutic efficacy of cytokines can be significantly improved. Specifically, nanoparticles control cytokine release by anchoring cytokines or utilizing mRNA-encoded cytokines and effectively activate immune cells to enhance local immune responses (139). These innovations are expected to overcome the blood-brain barrier for efficient drug delivery, break the tumor immunosuppressive microenvironment, and enhance anti-tumor immune responses.

Engineered nanomaterials are effective due to the BBB's high porosity and restricted lymph flow within the GBM, facilitating a buildup of medication in the brain. In addition, the use of nanomaterials facilitates the extended and controlled release of antigens or adjuvants, accurate targeting of BBB endothelial cells and the cellular introduction of RNA-centric vaccines, offering potential solutions to the challenges these vaccines face (140).

Overcoming the dual barriers of the BBB and blood-tumor barrier (BTB) in GBM remains a major therapeutic challenge, due to their structural complexity and adaptive resistance mechanisms. Nonetheless, pharmaceutical distributing methods that employ nanoparticles for cell transport and virus delivery, as well as accurate ultrasound, magnetic fields and nasal medication administration, enhance the permeability of the BBB and BTB, thus providing unique advantages for treating GBM (141).

Song *et al* (142) constructed a biomimetic nano-drug delivery system targeting GBM [red blood

cell membrane-functionalized albumin nanoparticles (RFANPs)] to deliver Lomitorpeptide (LMP), demonstrating that LMP RFANPs exhibited excellent anti-GBM activity in tumor-bearing mice, significantly improving targeted drug delivery efficiency. In a subsequent study (143), the researchers engineered a biomimetic nanotherapeutic system coated with GBM cell membranes. This platform co-delivered HuaChanSu and photoresponsive Cu2-xSe nanoparticles across the blood-brain barrier. Upon near-infrared irradiation, Cu2-xSe generated localized hyperthermia for photothermal ablation, while HuaChanSu exerted cytotoxic effects by arresting the cell cycle at G2/M phase and triggering mitochondrial apoptosis. The GBM membrane coating not only enhanced tumor-specific accumulation through homotypic binding but also mitigated immune clearance, thereby amplifying the synergy between chemotherapy and photothermal therapy. Ruan *et al* (144) utilized the Cas12a gene editing function to create an effective CRISPR/Cas12a nanodrug-targeting GBM therapy based on nanocapsules; The CRISPR/Cas12a system is able to extend blood half-life, effectively cross the BBB, active tumor targeting and selective release.

Physical therapy. The tumor treating (TT)Fields signify a groundbreaking technique in the field of physical therapy. Unveiling the results of the EF-14 clinical trials for electric field therapy in 2017 ignited widespread enthusiasm and renewed hope in the treatment of GBM (145).

TTFields employs a mild treatment strategy to avert the division and multiplication of tumor cells, utilizing the soft, varying electric fields present at the tumor site. The fundamental idea involves applying electric fields to modulate the motion of charged molecules, thereby obstructing the creation and disintegration of microtubules during cell division, which in turn leads to cell death by apoptosis. TTFields principally hinders the gathering of microtubule proteins during cell division, thereby preventing the formation of mitotic spindles and changes in cell membrane potential caused by electric fields, which in turn initiates the apoptosis signaling route (146).

Studies suggest that electrical fields selectively induce cell cycle arrest and apoptosis in dividing cells, while sparing non-dividing cells (147). During metaphase, microtubules undergo changes in oscillation, rotation and structure due to differing electric field pressures from TTFields, affecting spindle formation, leading to mitotic stops, delayed responses and irregular chromosome splitting. As a result, tumor cells stray from their mitotic path, resulting in reduced growth rates or the formation of non-diploid progeny cells (148).

Focused ultrasound technology (FUS). FUS utilizes the placement of microbubbles and the amplification of acoustic waves to create mechanical effects on blood vessels, leading to a brief breach of the BBB and subsequent biological repercussions. This method generates thermal and mechanical effects in specified zones through intense concentrated ultrasound, causing protein disintegration and cellular demise, with the goal of eliminating tumor tissue.

Initial results suggested that specific ultrasound may trigger an immune response. A study on mice with GBM models demonstrated that under specific ultrasound, tumor antigens are released, prompting immune-cell activation and shifting the tumor's surrounding environment from frigid to warm states (149). Strong ultrasound may induce radiosensitization due to tumor resistance in hypoxia; hence, increased blood flow and oxygen concentration can heighten the responsiveness to radiotherapy (150). In addition, localized ultrasound-detecting microbubbles can obstruct tumor blood vessels, leading to low oxygen levels and the demise of cancer cells (151). By precisely excising tumors using ultrasound, reducing their size, momentarily opening the BBB and enhancing the effectiveness of chemotherapy, targeted therapy and immunotherapy drugs, superior outcomes are achieved (152).

Magnetic hyperthermia-mediated cancer therapy (MHCT). Magnetic hyperthermia is a term that describes the generation of heat via the twisting of particles, reduction in Eddy currents, hysteresis and the turning of magnetic particles within a volatile magnetic field. MHCT utilizes magnetic nanoparticles in cancer tissues exposed to a varying magnetic field, thereby heating the tumor to achieve therapeutic goals (153). Studies showed that MHCT is an effective treatment that reduces tumor cell growth and elevates survival rates in initial tumor models. MHCT can be employed independently as a therapy for GBM or in conjunction with additional methods (154). Currently, MHCT is regarded as a promising and non-intrusive treatment method, adept at administering thermotherapy to tumors requiring surgical intervention.

The thermal attributes of drug-treated nanocarriers can temporarily breach the BBB, thereby increasing the amount of medication injected at the targeted tumor site and enhancing the therapeutic advantages of hyperthermia coupled with chemotherapy (155). Research indicates that MHCT increases the drug resistance of GBM to temozolomide, thereby enhancing the absorption of the drug by cancerous cells with decreased MGMT expression (156). Thus, the utilization of hyperthermia may act as a tactic to mitigate chemotherapy resistance in GBM, thereby improving the effectiveness of chemotherapy.

7. Summary and outlook

GBM, as a highly malignant brain tumor, is characterized by highly complex molecular profiles, IDH mutations, MGMT promoter methylation status and other genetic alterations (157). No major breakthroughs in therapeutic outcomes have been achieved since the 2000s (158). The current state of the field is characterised by the following: On the diagnostic side, imaging techniques and molecular testing tools continue to advance, but early and accurate diagnosis remains a challenge. Therapeutically, combination therapy of surgical resection, radiotherapy and chemotherapy is still the mainstay, but the efficacy is limited and the median survival of patients remains short. Although research on the molecular mechanisms of GBM has made some progress and identified key gene mutations and signalling pathway abnormalities, they have not yet been translated into effective clinical treatment strategies.

In order to further break through the GBM treatment dilemma, future research needs to focus on the following directions: Developing sensitive and specific biomarkers

based on the molecular features of GBM; exploring the tumour microenvironment of GBM in depth to develop more targeted immunotherapy strategies; and integrating genomic, epigenomic, proteomic and spatial transcriptomic data to construct dynamic molecular typing frameworks to guide individualized treatment. Immunometabolic regulation, engineered cell therapy, microbiome intervention to explore the impact of gut-brain axis regulation on the immune response of GBM, penetration of the BBB, development of a real-time monitoring platform based on liquid biopsy (e.g., ctDNA, exosomes) and tracking the clonal evolution and drug resistance mechanisms during the treatment process are also future tasks. In addition, an international collaborative GBM multi-omics database will be established and clinical images, pathological sections and organoid drug sensitivity data will be integrated to predict therapeutic responses using deep learning. The cross-application of physics and synthetic biology will also be explored. Advanced experimental techniques and models will be further developed to more realistically simulate tumour properties. This may bring substantial survival hope to patients with GBM.

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Authors' contributions

HXH and AD were responsible for the collection and organization of literature. JL and HYH were accountable for the analysis and assessment of data. PF was in charge of organizing and writing the article. GT was tasked with drawing illustrations. YZ and XL helped GT with the image conception and color mixing software operation. HY and BZ were responsible for writing the first draft of the manuscript. WL contributed by generating Table I. GY was responsible for the final revision and proofreading. All authors actively contributed to different aspects of this study and jointly reviewed and approved the content of the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

In the preparation of this work, chatgtp3.5 as well as ERNIE Bot 4.0 were used to linguistically edit the already written manuscript in order to make the manuscript more rigorous and standardised in this one aspect of language. After using this tool, the content was reviewed and edited as needed and the authors take full responsibility for the content of the publication.

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