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# Glioblastomas - Study Using Molecular Markers

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**ABSTRACT**

Glioblastoma is a lethal tumor that can develop in the central nervous system. The most serious type of brain cancer is known as glioblastoma multiforme (GBM). This work aims to emphasize the usage of different glioblastoma markers during the diagnosis process and the treatment of the GBM. And also this may focus on the changes that are often associated with GBM pathogenesis and understanding the significance of glioblastoma markers, as well as their involvement in numerous critical cellular signaling pathways, can help direct potential research toward novel GBM treatments.

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## Introduction

Glioblastoma is a sort of malignant growth that can develop in the central nervous system that is classified as a grade IV astrocytoma, which is a rapidly-growing and aggressive cancer. Glioblastoma starts from astrocytes, which are cells that feed on nerve cells. Glioblastoma tumors produce their blood, which helps in their growth. They can easily penetrate normal brain tissue. Glioblastoma, also known as glioblastoma multiform (GBM), is the most serious form of brain cancer [1].

GBM is a fatal disease with a sad prognosis, short-term median patient survival, and adverse treatment outcomes. It has a complex etiology that includes genetic mutations and mutations in several important cell pathways involved in cell proliferation, survival, migration, and angiogenesis. As a result, better knowledge of GBM etiology is essential for the development of effective treatment [2].

CD133, CD44, CD15, CD70 (CD27 L), S100A4, ALDH1A3, Nanog, OCT-4, SOX-2, and Nestin are some of the potential symptoms an approach for detecting glioma stem cells (GSCs). GSC indicators play an essential purpose in malignancy. MicroRNAs (miRNAs) are very high sensitivity and specificity indicators that might be used to both diagnose and predict cancer [3].

RTK Receptor Tyrosine Kinase (RTK) Expression in GB

GBM tumors are subdivided into several cell subtypes with distinct genetic signals and show abnormal activation of many signaling pathways, especially those linked to receptor tyrosine kinases (RTKs) that regulate glioma cell growth, survival, migration, invasion, and angiogenesis. G-protein-coupled receptors and calcium channels are the two non-canonical types of RTK signaling detected in GBM [4].

More than 80% of key GBMs include RTK mutations, which include EGFR, PDGFRA, basic fibroblast growth factor receptor 1 (FGFR-1), and insulin-like growth factor receptor (IGFR-). 1).The RAS/RAF/MAPK pathway, which leads to cell proliferation, differentiation, and migration, as well as the PI3K/AKT/mTOR method, which is highly effective in promoting cell proliferation and survival through cell cycle progression and prevention of apoptosis, are two main symptoms RTK techniques utilized in gliomas. The PTEN implant component, which suppresses this process, controls PI3K activity. PTEN deficiency may result in significant overproduction, which may be a major source of resistance to EGFR treatment [5-7].

The most common genetic mutations include EGFR mutations, reorganization, further consolidation, and environmental enhancement [8]. In clinical trials of people with GBM, EGFR antagonists weren't efficient [9-11]. Lack of response may be attributed to very small drug intrusion into the entire blood-brain barrier, which was found to change resistance to target RTKs, and intratumoral heterogeneity in GBM tumors [12,13].

When it comes to additional RTK mutations, high levels of PDGFRA have been found, and about half of these issues have also been able to increase EGFR and/or mutation [14]. Despite the relatively rare occurrence in GBM, mutations such as increased mesenchymal-epithelial transition factor (c-Met) and FGFR mutations were found in 2% of GBMs tested [15,16].

All of these functional genetic mutations can occur simultaneously in a few RTKs within a single GBM, as well as changes in the lower parts of the growth pathway for growth factor acquisition.

The most powerful oncogenic mechanism for GBM is PI3K / AKT / mTOR, which can be activated by converting the catalytic domain (PIK3CA) or PI3K (PIK3R1) [17]. It was found that more than 10% of GBMs have PIK3R1 mutations, which have not been reported as commonly expressed in any other hate [18]. AKT categorization was found to be a sign for detecting a subgroup of GBM patients who reacted to carmustine (BCNU)/CCNU and PI3K/AKT/mTOR pathway antagonists [19]. Recent studies have found that the gene for tumor suppressor NF1, which produces the neurofibromin (RAS negative regulator), is altered or removed from 15% to 18% of the primary GBM (mesenchymal subclass) [20].

**The Tyrosine Kinase Receptors**

RTKs are a kind of membrane protein that works as a sensor for external signaling molecules such as growth factors, cytokines, hormones, neurotrophic factors, etc. RTKs respond to ligand activation by signaling via two key downstream pathways: Ras/MAPK/ERK and Ras/PI3K/AKT [21]. Cell division, survivability, specialization, and angiogenesis are all influenced by these mechanisms. EGFR, PDGFR, FGFR, IGF-1R, VEGFR, and hepatocyte growth factor receptor (HGFR/c-MET) are the 6 main tyrosine kinase receptors.

Tyrosine kinase receptors have the same structure as ligand-binding domains, hydrophobic transmembrane domains, and intracellular tyrosine kinase domains. Ligand contact stimulates them, causing receptor dimerization and tyrosine kinase domain autophosphorylation. This causes two important downstream signaling pathways to be activated: Ras/MAPK/ERK and Ras/PI3K/AKT [22-28]. RTKs and their ligands are prospective therapeutic targets for the treatment of GBM due to their capability to stimulate downstream signaling pathways involved in proliferation, invasiveness, survival, and angiogenesis.

**RTK Signal Transduction Cascade Biomarkers**

**PDGFR**

PDGFR signaling is crucial in normal tissue development, and its imbalance causes oncogenesis. GBMs frequently have a PDGF autocrine loop that is not present in normal brain tissues [29]. PDGFRα (platelet-derived growth factor receptor alpha) is the second most frequently increased RTK in GBM after EGFR. GBM has been demonstrated to express all PDGF ligands (PDGF-A, PDGF-B, PDGF-C, and PDGF-D), as well as the two cell surface receptors PDGFR-α and PDGFR-β [30].

**VEGFR**

The angiogenesis protein VEGF has been found to promote capillary permeability. It has also been shown that malignant transformation increases VEGF Expression level [31]. Hypoxia-inducible transcription factors (HIF1 and HIF1) translocate to the nucleus and activate the VEGF gene under hypoxic conditions. When VEGF is activated, angiogenesis increases to compensate for hypoxia [32]. GBM tumors are frequently hypoxic, with elevated VEGF production, which contributes to the irregular vasculature associated with GBM. GBM tissues have been found to exhibit extremely high levels of VEGF expression, which has been linked to an increase in the expression of the VGFR receptor VEGFR2 [33,34].

**EGFR**

EGFR is a member of a family of four tyrosine kinases that includes ErbB1 (EGFR, HER1), ErbB2 (Her-2), ErbB3 (Her-3), and ErbB4 (HER-4) (Her-4). EGFRs promotes proliferation and have been linked to glioblastoma etiology and treatment resistance [35]. ErbB2/HER-2 mutations were also found in 8–41% of GBM cases [36]. In GBM, a mutant EGFR variant III (EGFRvIII) is widely produced and is constitutively induced in a ligand-independent manner, resulting in cell proliferation and survival. Despite the EGFRvIII's growth-promoting capabilities, its expression has been associated with increased overall survival in patients [37,38]. This can be understood by the fact that EGFRvIII is a neoantigen, which may induce an immunological response.

**FGFR**

There are 22 FGFs (fibroblast growth factors) and four distinct FGF receptors in humans (FGFR1, 2, 3, and 4). FGF2 has been demonstrated to increase the growth of cultured GBM cell lines, whereas FGFR signaling inhibition via RNA interference or antibody blocking reduced GBM cell proliferation. . FGFR1 has also been observed to be expressed at higher levels in brain tumors when compared to neighboring normal brain tissue, implying that this receptor plays a role in carcinogenesis. FGF5 has even been discovered to be upregulated in GBM, and its expression has been linked to increased proliferation.

**IGF-1R**

IGF-1R was shown to be highly expressed in GBM, and this upregulation was associated with decreased survival and lower responsiveness to temozolomide, implying a role for IGF-1R signaling in GBM pathogenesis.

**HGFR/c-ME**

The activating ligand for HGFR/c-MET that has been demonstrated to be released by brain tumor cells is scattered factor (SF)/hepatocyte growth factor (HGF) In cancer cells and vascular endothelial cells, HGFR/c-MET expression and activation result in cellular proliferation and invasion. The relationship of HGFR/c-MET with proliferation and survival suggests that it could be used as a target for GBM therapy.

**IDH Mutations**

IDH1 and IDH2 gene codes two key metabolic enzymes: isocitrate dehydrogenase 1 & 2. These proteins do the oxidative carboxylation of isocitrate to alpha-ketoglutarate in the Krebs cycle, culminating in the production of NADPH [39,40]. The development of the oncometabolite 2-hydroxyglutarate is aided by mutations in these IDH genes [41,42].

Gliomas with IDH mutations are a separate pathological disease that emerges virtually exclusively in gliomas with EGFR amplification and chromosome 10 loss and develops in the context of TP53 mutation or 1p/19q chromosomal deletion. Furthermore, IDH-mutant tumors have been associated with significant epigenetic abnormalities, such as DNA methylation disorders, which exhibit a dramatic pattern of hypermethylation of certain DNA promoter regions known as the glioma-CpG island methylator phenotype (G-CIMP). The IDH route is not used by wild-type IDH gliomas, including pilocytic astrocytomas and primary GBMs (G-CIMP).

**TP53/MDM2/p14ARF Pathway**

The tumor suppressor gene TP53 encodes a p53 protein that controls target genes associated with cell arrest in the G1 and/or G2 phases, cell death and differentiation, DNA repair, and neovascularization [43-45]. TP53 can be inactivated indirectly by mutation or deletion, or directly through damage to collaborating genes [46]. The oncoprotein MDM2 suppresses p53 function by ubiquitinating it and causing it to be degraded by the proteasome. In addition, the p1 protein functionally antagonizes MDM2 and,

as a result, inhibits p53 silencing [47].

**MGMT Methylation**

MGMT encoding promoter O6 -methyl guanine-DNA methyltransferase is a DNA repair enzyme that protects cells from alkylating chemicals by preventing G: CA: T gene alterations. [48]. MGMT promoter methylation disorders are related to transcriptional suppression of the MGMT gene and loss of MGMT expression, which leads to reduced DNA repair and retention of alkyl groups, making alkylating drugs more effective in patients with MGMT promoter hypermethylation. The methylation level of the MGMT promoter is a powerful predictor of responsiveness to alkylating medications and one of the most significant prognostic factors in GBMs.

**P16ink4a/CDK4/RB1 Pathway**

The CDKN2A binds specifically to CDK4 cyclin and inhibits the CDK4/cyclin D1 complex, preventing the cell cycle from entering S-phase [49]. As a result, abnormal activity of any of the p16INK4a, CDK4, or RB1 genes could result in the loss of typical RB1 function. This route is frequently inactivated in both primary and secondary GBMs.

**Immune Checkpoints**

In addition to alterations in cell communication and growth factors, the capacity of the GBM to evade immune system surveillance contributes to its aggressive nature. Through the generation of immunosuppressive cytokines, GBM has found a way for dampening the immune response [50]. The antigens cytotoxic T-lymphocyte (CTLA 4) & programmed cell death protein (PD-1) have an influence on immune reduction [51].

CTLA-4 is exclusively located on T cells and controls T-lymphocyte stimulation in the initial stages by interfering with the costimulatory protein CD28 for B7 ligand binding [52,53].

Furthermore, PD-1 modulates immunity at several stages of the immune response, influencing T-cell activity in peripheral tissues [54]. PD-L1, a PD-1 ligand, and CTLA-4 have high levels of mRNA expression in mesenchymal GBMs, suggesting a relationship between immune checkpoint proteins and GBM severity [55].

According to findings from phase III research utilizing a dendritic cell vaccine (DCVax-L), CTLA-4 activity can predict survival in GBM patients, suggesting that CTLA-4 might be used as a biomarker for treatment response. A randomized phase II/III study of ipilimumab in combination with TMZ in patients with early diagnosed glioblastoma is also being planned by the RTOG.

**Several Glioblastoma Markers**

**a) NESTIN**

Nestin has recently been found as an endothelial cell-enriched protein in all adult vascular beds. Nestin expression in tumors is not confined to cancer cells but also occurs in newly formed tumor vasculature and it is a useful marker of continuing angiogenesis and CSCs [56,57]. In some malignancies, nestin expression is linked to metastasis and aggressive development [58].

Nestin regulates proliferation, stemness, and invasion in glioblastoma cells via modifying HSC71 (gene HSPA8). As a result, inhibiting Nestin and/or HSC71 could be a useful molecular target therapy for glioblastoma [59].

The activation of the KRAS/Notch route promotes NestinPos GSC proliferation, whereas the activation of the Akt/PI3K and p53 pathways promotes radiation resistance. Glioblastoma cells were sensitized to TMZ by suppressing miR-381, which prevents stemness factors such as Nestin. Furthermore, miR-423-5p boosted Nestin expression in GSCs by suppressing its target gene (ING-4) and induced glioblastoma cells to be more resistant to TMZ. As a result, miR-423-5p or miR-381 inhibition in conjunction with TMZ intervention may be a good therapeutic method for decreasing GSC proliferation.

**B) SOX-2**

SOX-2, also known as sex-determining region Y (SRY)-box 2, is a transcription factor in the sry-related high-mobility group (HMG) box (SOX) family. In glioblastomas, SOX-2 is overexpressed [60]. SOX-2 is demonstrated to play a function in cancer cell metastasis, proliferation, apoptosis, carcinogenesis, and invasion [61].

SOX-2 has been identified to be crucial for growth and survival in glioma and is linked to relapse following chemotherapy or radiotherapy [62]. In developed glioblastoma cells, SOX-2 suppression induces cellular senescence. Furthermore, SOX-2 overexpression is required for GSC maintenance in addition to enhancing invasiveness and migration. One of the most crucial proteins in GBM treatment resistance is this one. Because of the crucial role, it plays in GSC maintenance, inducing resistance to chemotherapy and radiotherapy, the CD133Pos/SOX-2 alliance is appropriate for glioblastoma treatments [63]. Furthermore, SOX-2 has demonstrated different roles for self-renewal in GSCs through its association with FOXG1, one of the most overexpressed genes in glioblastoma [64].

SOX-2 was a primary target of miR-429, which has been identified to function in glioblastoma as either an oncogene or a tumor suppressor. miR-429, by directly targeting SOX-2, had a preventative effect on the proliferation and invasion of glioblastoma cells. By targeting SOX-2-Wnt/-catenin, miR-126-3p sensitized glioblastoma cells to TMZ. Their findings revealed that miR-126-3p suppresses SOX-2 expression, hence blocking the Wnt/-catenin pathway. Similarly, another study found that miR-145 increased the chemosensitivity of GSCs to desmethoxycurcumin (DMC) through targeting SOX-2-Wnt/-catenin.GSC state characteristics and maintenance have also been demonstrated to be hindered by miR-34a's suppression of SOX-2 and Nanog. Additionally, SOX-2 was discovered to be a direct target of miR-124, resulting in decreased migration and self-renewal in GSCs.

**c) CD133**

CD133 acts as a cancer stem cell marker in glioblastoma (GBM) cells that can commence neurosphere growth and produce heterogeneous tumors. However, even though CD133-negative cells exhibit identical features, there is no hierarchical relationship between CD133-positive and CD133-negative cells that comprise the neurospheres. Indeed, CD133 emerges in an interconvertible state, switching between the cytoplasm and the plasma membrane of neurosphere cells. The use of lentivirus-mediated short hairpin RNA to silence CD133 in human GBM neurospheres affects neurosphere cell self-renewal and tumorigenicity [65].

According to the studies, the more the expression of CD133 in GBM patients, the bigger the malignancy potential of the cells. Based on the literature assessment, it is clear that CD133 is critical for the malignant oncogenic potential of GBM stem cells since its silencing inhibits both self-renewal and tumorigenic capacity.

However, certain CD133-negative cells can produce aggressive cancers, which is a little conflicting finding [66].

**d) CD44**

CD44 is a transmembrane molecule that has many isoforms and is overexpressed in GBM, where it promotes tumor development through interactions with the tumor microenvironment. CD44 increases tumor cell invasion, proliferation, and resistance to conventional chemoradiation therapy, promoting GBM aggressiveness. In GBM, CD44 shows an inhibitory influence also [67].

**e) CD15**

CD15 is a disaccharide that contains 3-fucosyl-N-acetyllactosamine and is also known as stage-specific embryonic antigen 1 [68-70]. CD15 has been demonstrated to be highly expressed on pluripotent SCs and neural stem cells (NSCs) in the adult brain, where it is thought to play a role in cell-cell interaction throughout neuronal maturation [68,71]. PN subtype GSCs have a high level of CD15 expression on the cell surface, associated with CD133.

CD15 expression was observed to be increased in non-CSCs under hypoxic circumstances. Hypoxia does, in fact, trigger sphere formation in glioblastoma-sorted non-CSCs, and those freshly formed spheres are strongly expressed in SC markers such as CD15. This suggests that CD15Pos GSCs can be activated throughout dedifferentiation in a hypoxic environment and that this interaction between non-GSCs and GSCs may promote cancer progression. The therapeutic doses of TMZ significantly raised the expression of numerous gliomas stem cell markers, such as CD15 and CD133, in vitro and in vivo glioblastoma cells can restart GSC features, including an increase in the expression of CD133 and CD15, following continued TMZ exposure. Similarly, N-(p-coumaroyl) serotonin therapy resulted in a significant dose-dependent increase in the number of CD15 markers in GBM [72].

**f) OCT4**

OCT-4 expressed in astrocytic brain cancers. OCT-4, like GLI1, has a transcriptional regulatory mechanism involving secreted phosphoprotein 1. (SPP1). Both OCT-4 and GLI1 are overexpressed in glioma-initiating cells and glioblastoma, and this axis maintains the stemness phenotype through binding to the SPP1 gene [73]. GLI1 is a member of the SHH pathway that is overexpressed in glioblastoma tumors. It upregulates not just OCT-4 but also Nanog and SOX-2, whereas its inhibition downregulates OCT-4 and Nanog. GLI1activated by the Akt pathway. [74].GLI1 inhibition causes glioblastoma growth suppression [75]. The crosstalk between Akt and OCT-4 was validated. They found that Akt might indirectly influence OCT-4 mRNA levels, transcriptional activity, and protein stability in ESCs. Other research has found that knocking down OCT-4 in embryonic cancer cells increased Akt expression levels, whereas inhibiting the Akt pathway increased OCT-4 expression in GSCs [76,79]. These findings point to a negative regulatory connection between Akt and OCT-4.

**g) CD70 (CD27L)**

CD70 association with CD27 regulates the activity of cytotoxic T lymphocytes, extending the life of mice with renal cell carcinoma [81-83].The co-expression of CD70 and CD163 in M2 macrophages was discovered to be linked to shorter survival of GBM patients. These findings suggest that CD70 increases tumor immunosuppression and aggressiveness by activating and recruiting tumor-associated macrophages [80].

**h) S100A4**

This protein is a trophic factor with a wide range of functions discovered in the CNS [84,85]. S100A4 is significantly overexpressed in the injured human brain [86].S100A4 interacts with ErbB4 ligand and neuregulin (NRG), and this signaling is important for neuroprotection in a damaged or wounded brain. In numerous malignancies, including glioblastoma, S100A4 has been identified as a prognostic marker, metastasis promoter, and regulator [87].

S100A4 played a role in glioma progression with MES characteristics. A recent study offered more solid clarification and definitive evidence for S100A4's roles as a crucial regulator and a novel marker of GSCs. S100A4Pos cells were demonstrated to be capable of beginning tumors and generating spheres, and S100A4 is required for GSC self-renewal. While the molecular mechanism that promotes GSC self-renewal and maintenance remains unknown, it appears that S100A4 is involved in the upstream processes of EMT and MES transition [87]. S100A4 knockdown prolonged the anti-VEGF treatment profile, reducing glioblastoma resistance to antiangiogenic therapy. As a result, inhibiting S100A4 may be a potential strategy for limiting glioma malignancy [88,89]. CCAAT/enhancer-binding protein (C/EBP) inhibition significantly reduced S100A4 levels in glioblastoma cells, resulting in inhibitions of growth, transformation capacity, and migration. Thus, targeting C/EBP in glioblastoma cells is therapeutically advantageous to inhibit the S100A4 gene [90].

**i) ALDH1A3**

ALDH1A3 has been identified as a marker that promotes GSCs and corresponds with the MES phenotype and invasion in human glioblastoma [91-94]. The PN subtype was more prevalent in gliomas with reduced ALDH1A3 expression and ALDH1A3 inhibition decreased the growth of PN GSCs [95]. ALDH1A3 was also found to be not only connected with the MES lineage of GBM but also to be a critical driver in promoting MES subtype differentiation [96].

Transcriptional factor FOXD1 has direct control on ALDH1A3 transcription. FOXD1-ALDH1A3 signaling was identified as a critical route in the self-renewal and tumorigenicity of MES GSCs. As a result, it offers a potential new molecular target for treating GBM [97]. Where it increases stem cell-like qualities by promoting the production of tissue transglutaminase (tTG), an enzyme previously associated with the onset and progression of aggressive cancers tTG promotes the aggressiveness of MES GSCs in glioblastoma cells by increasing proliferation, self-renewal, and survival. Inhibiting this enzyme with TMZ or radiotherapy reduced cell growth and increased cell death. These findings suggest that ALDH1A3 plays a new role in the aggressive MES GSCs phenotype via tTG overexpression.

**j) NANOG**

Nanog has been identified as a new hedgehog (HH) and glioma-associated oncogenes (GLI) signaling pathway mediator that is required for glioblastomas. In patients with low- and high-grade gliomas, Nanog expression levels beyond a particular threshold were connected to a worse chance of survival [98]. A pathologically significant connection with Nanog and CD133 co-expression they found that Nanog overexpression and its strong association with the undifferentiated condition of glioblastoma led to carcinogenesis by keeping the tumor undifferentiated. Nanog inhibition may prevent glioblastoma carcinogenesis, and targeting Nanog may be an effective way to improve therapeutic intervention for poorly differentiated glioblastoma. Similarly,

under hypoxic conditions, Nanog and CD133 were found to have a favorable association. In addition to CD133, hypoxia consistently increased Nanog expression in glioblastoma cell types [99,100].

## Conclusion

According to the above-mentioned information, Glioblastoma Markers can be used to detect the previously described alterations in a minimally invasive method. . These indications can also be used to evaluate if a person's prognosis is favorable or unfavorable, as well as to identify individuals who do not react to treatment.

## References

1. Mayo Foundation for Medical Education and Research (2020). Glioma. Mayo Clinic. Retrieved from https://www.mayoclinic.org/diseases-conditions/glioblastoma/cdc-0350148#:~:text=Glioblastoma%20is%20an%20aggressive%20type,also%20known%20as%20glioblastoma%20multiforme.
2. Pearson J, Regad T (2017) Targeting cellular pathways in glioblastoma multiforme. Sig Transduct Target Ther 17040.
3. Hassn Mesrati M, Behrooz AB, Y Abuhamad A, Syahir A (2020) Understanding Glioblastoma Biomarkers: Knocking a Mountain with a Hammer Cells. 9: 1236.
4. Tilak M, Holborn J, New LA, Lalonde J, Jones N (2021) Receptor Tyrosine Kinase Signaling and Targeting in Glioblastoma Multiforme. Int J Mol Sci. 22:1831.
5. H Ohgaki, P Kleihues (2009) Genetic alterations and signaling pathways in the evolution of gliomas. Cancer Science 100: 2235-2241.
6. I K Mellinghoff, MY Wang, I Vivanco, et al. (2005) Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. The New England Journal of Medicine 353: 2012-2024.
7. E Padfield, H P Ellis, K M Kurian (2015) Current therapeutic advances targeting EGFR and EGFRvIII in glioblastoma. Frontiers in Oncology 5: 5.
8. F B Furnari, T F Cloughesy, W K Cavenee, P S Mischel (2015) Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma. Nature Reviews Cancer 15: 302-310.
9. D A Haas-Kogan, M D Prados, T Tihan ,et al. (2005) Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib. Journal of the National Cancer Institute 97: 880-887.
10. A M P Omuro, S Faivre, E Raymond (2007) Lessons learned in the development of targeted therapy for malignant gliomas. Molecular Cancer Therapeutics 6: 1909-1919.
11. E Franceschi, G Cavallo, S Lonardi, et al. (2007) Gefitinib in patients with progressive high-grade gliomas: a multicentre phase II study by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). British Journal of Cancer 96: 1047-1051.
12. S Sathornsumetee, D A Reardon, A Desjardins, J A Quinn, J J Vredenburgh, et al. (2007) Molecularly targeted therapy for malignant glioma. Cancer 110: 13-24.
13. C A Del Vecchio, C P Giacomini, H Vogel, et al. (2013) EGFRvIII gene rearrangement is an early event in glioblastoma tumorigenesis and expression defines a hierarchy modulated by epigenetic mechanisms. Oncogene 32: 2670-2681.
14. F B Furnari, T F Cloughesy, W K Cavenee, P S Mischel, (2015) Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma. Nature Reviews Cancer 15: 302-310.
15. D Singh, J M Chan, P Zoppoli ,et al. (2012) Transforming fusions of FGFR and TACC genes in human glioblastoma. Science 337: 1231-1235.
16. R Abounader, J Laterra, (2005) Scatter factor/hepatocyte growth factor in brain tumor growth and angiogenesis. Neuro-Oncology 7:436-451.
17. J T Huse, K D Aldape, (2014) The evolving role of molecular markers in the diagnosis and management of diffuse glioma. Clinical Cancer Research 20: 5601-5611.
18. Cancer Genome Atlas Research Network, Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature, 455:1061-1068, 2008.
19. A Joy, A Ramesh, I Smirnov, et al. (2014) AKT pathway genes define 5 prognostic subgroups in glioblastoma. PLoS ONE 9: e100827.
20. D W Parsons, S Jones, X Zhang, et al. (2008) An integrated genomic analysis of human glioblastoma multiforme. Science 321: 1807-1812.
21. Regad T (2015) Targeting RTK signaling pathways in cancer. Cancers (Basel) 7:1758-1784.
22. Scaltriti M, Baselga J (2006) The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res 12: 5268-5272.
23. Burgess AW, Cho HS, Eigenbrot C, Ferguson KM, Garrett TP, et al. (2003) An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors. Mol Cell 12: 541-552.
24. Roskoski R Jr (2008) VEGF receptor protein-tyrosine kinases: structure and regulation. Biochem Biophys Res Commun 375: 287-291.
25. Nazarenko I, Hede SM, He X, Hedren A, Thompson J, et al. (2012) PDGF and PDGF receptors in glioma. Ups J Med Sci 117: 99-112.
26. Andrae J, Gallini R, Betsholtz C (2008) Role of platelet-derived growth factors in physiology and medicine. Genes Dev 22: 1276-1312.
27. Ma PC, Maulik G, Christensen J, Salgia R (2003) c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev 22: 309-325.
28. Baserga R, Hongo A, Rubini M, Prisco M, Valentinis B (1997) The IGF-I receptor in cell growth, transformation and apoptosis. Biochim Biophys Acta 1332: F105-F126.
29. Lokker NA, Sullivan CM, Hollenbach SJ, Israel MA, Giese NA (2002) Platelet-derived growth factor (PDGF) autocrine signaling regulates survival and mitogenic pathways in glioblastoma cells: evidence that the novel PDGF-C and PDGF-D ligands may play a role in the development of brain tumors. Cancer Res 62: 3729-3735.
30. Nazarenko I, Hede SM, He X, Hedren A, Thompson J, et al. (2012) PDGF and PDGF receptors in glioma. Ups J Med Sci 117: 99-112.
31. McMahon G (2000) VEGF receptor signaling in tumor angiogenesis. Oncologist; 5 (Suppl 1): 3-10.
32. Shibuya M (2001) Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. Cell Struct Funct 26: 25-35.
33. Steiner HH, Karcher S, Mueller MM, Nalbantis E, Kunze S,et al. (2004)Autocrine pathways of the vascular endothelial growth factor (VEGF) in glioblastoma multiforme: clinical relevance of radiation-induced increase of VEGF levels. J Neurooncol 66: 129-138.
34. Joensuu H, Puputti M, Sihto H, Tynninen O, Nupponen NN (2005) Amplification of genes encoding KIT, PDGFRalpha and VEGFR2 receptor tyrosine kinases is frequent in glioblastoma multiforme. J Pathol 207: 224-231.
35. Huang PH, Xu AM, White FM (2009) Oncogenic EGFR

signaling networks in glioma. Sci Signal 2: 6.
36. Zhang C, Burger MC, Jennewein L, Genssler S, Schonfeld K, et al. (2015) ErbB2/HER2-Specific NK Cells for Targeted Therapy of Glioblastoma. J Natl Cancer Inst 108.
37. Montano N, Cenci T, Martini M, D'Alessandris QG, Pelacchi F, et al. (2011) Expression of EGFRvIII in glioblastoma: prognostic significance revisited. Neoplasia 13: 1113-1121.
38. Heimberger AB, Suki D, Yang D, Shi W, Aldape K (2005) The natural history of EGFR and EGFRvIII in glioblastoma patients. J Transl Med 3: 38.
39. X Xu, J Zhao, Z Xu, et al. (2004) Structures of human cytosolic NADP-dependent isocitrate dehydrogenase reveal a novel self-regulatory mechanism of activity. Journal of Biological Chemistry 279: 33946-33957.
40. Z J Reitman, H Yan, (2010) Isocitrate dehydrogenase 1 and 2 mutations in cancer: alterations at a crossroads of cellular metabolism. Journal of the National Cancer Institute 102: 932-941.
41. L Dang, DW White, S Gross, et al, (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 462: 739-744.
42. W Xu, H Yang, Y Liu, et al. (2011) Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. Cancer Cell 19:17-30.
43. KH Vousden, DP Lane (2007) p53 in health and disease. Nature Reviews Molecular Cell Biology 8: 275-283.
44. Bögler, H-J S Huang, P Kleihues, WK Cavenee (1995) The p53 gene and its role in human brain tumors. Glia 15: 308-327.
45. C Gomez-Manzano, J Fueyo, A P Kyritsis, et al. (1996) Adenovirus-mediated transfer of the p53 gene produces rapid and generalized death of human glioma cells via apoptosis. Cancer Research 56: 694-699.
46. H Ohgaki, P Kleihues (2007) Genetic pathways to primary and secondary glioblastoma. American Journal of Pathology 170: 1445-1453.
47. F J Stott, S Bates, M C James, et al. (1998) The alternative product from the human CDKN2A locus, p14 (ARF), participates in a regulatory feedback loop with p53 and MDM2. EMBO Journal 17: 5001-5014.
48. M E Hegi, A C Diserens, T Gorlia, et al. (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. New England Journal of Medicine 352: 997-1003.
49. C J Sherr, J M Roberts, (1999) CDK inhibitors: positive and negative regulators of G1-phase progression. Genes and Development 13: 1501-1512.
50. Rayman AP, Richmond AL, Biswas K, Zhang R, Vogelbaum M, et al. (2016) Glioblastomas Induce T-Lymphocyte Death by Two Distinct Pathways Liebelt BD, Shingu T, Zhou X, Ren J, Shin SA, Hu J Glioma stem cells: signaling, microenvironment, and therapy," Stem Cells International 10: 7849890.
51. Krummel MF, Allison JP (1996) CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells," Journal of Experimental Medicine 183: 2533-2540.
52. Salama AKS, Hodi FS (2011) Cytotoxic T-lymphocyte-associated antigen-4. Clinical Cancer Research 17: 4622-4628.
53. Bloch O, Crane CA, Kaur R, Safaee M, Rutkowski MJ, et al. (2013) Gliomas promote immunosuppression through induction of B7-H1 expression in tumor-associated macrophages. Clinical Cancer Research 19: 3165-3175.
54. Parsa AT, Waldron JS, Panner A (2007) Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nature Medicine 13: 84-88.
55. Doucette T, Rao G, Rao A (2013) Immune heterogeneity of glioblastoma subtypes: extrapolation from the cancer genome atlas. Cancer Immunology Research 1: 112-122.
56. Nowak A, Grzegrzółka J, Paprocka M, Piotrowska A, Rys J, et al. (2017) Nestin-positive microvessel density is an independent prognostic factor in breast cancer. Int J Oncol 51: 668-676.
57. Nowak A, Grzegrzółka J, Kmiecik A, Piotrowska A, Matkowski R, et al. (2017) Role of nestin expression in angiogenesis and breast cancer progression. Int J Oncol 52: 527-535.
58. Niu C, He H, Li MW (2011) Correlation between glioblastoma stem-like cells and tumor vascularization. Oncol Rep 27: 45-50.
59. Matsuda Y, Ishiwata T, Yoshimura H, Hagio M, Arai T (2015) Inhibition of Nestin Suppresses Stem Cell Phenotype of Glioblastomas through the Alteration of Post-Translational Modification of Heat Shock Protein HSPA8/HSC71. Cancer Lett 357: 602-611.
60. Gopal K, Gupta N, Zhang H, Alshareef A, Alqahtani H, Bigras G, et al. (2015) Oxidative stress induces the acquisition of cancer stem-like phenotype in breast cancer detectable by using a Sox2 regulatory region-2 (SRR2) reporter. Oncotarget 7: 3111-3127.
61. Ren Z-H, Zhang C-P, Ji T (2016) Expression of SOX2 in oral squamous cell carcinoma and the association with lymph node metastasis. Oncol Lett 11: 1973-1979.
62. Vasquez JC, Huttner A, Zhang L, Marks A, Chan A, (2017) SOX2 immunity and tissue resident memory in children and young adults with glioma. J Neuro-Oncology 134: 41-53.
63. Song W-S, Yang Y-P, Huang C-S, Lu K-H, Liu W-H, et al. (2016) Sox2, a stemness gene, regulates tumor-initiating and drug-resistant properties in CD133-positive glioblastoma stem cells. J Chin Med Assoc 79: 538-545.
64. Bulstrode H, Johnstone E, Marqués-Torrejón MÁ, Ferguson KM, Bressan R, et al. (2017) Elevated FOXG1 and SOX2 in glioblastoma enforces neural stem cell identity through transcriptional control of cell cycle and epigenetic regulators. Genome Res 31: 757-773.
65. Brescia P, Ortensi B, Fornasari L, Levi D, Broggi G, et al. (2013) CD133 is essential for glioblastoma stem cell maintenance. Stem Cells 31: 857-869.
66. Ahmed SI, Javed G, Laghari AA, Bareeqa SB, Farrukh S, et al. (2018) CD133 Expression in Glioblastoma Multiforme: A Literature Review. Cureus 10: e3439.
67. Mooney KL, Choy W, Sidhu S, Pelargos P, Bui TT, et al. (2022) The role of CD44 in glioblastoma multiforme. Journal of Clinical Neuroscience 34: 1-5.
68. Yamamuro S, Okamoto Y, Sano E, Ochiai Y, Ogino A, et al. (2015) Characterization of glioma stem-like cells from human glioblastomas. Int J Oncol 47: 91-96.
69. Jin X, Kim LJY, Wu Q, Wallace LC, Prager BC, et al. (2017) Targeting glioma stem cells through combined BMI1 and EZH2 inhibition. Nat Med 23: 1352-1361.
70. Shen M, Hu P, Donskov F, Wang G, Liu Q, et al. (2014) Tumor-Associated Neutrophils as a New Prognostic Factor in Cancer: A Systematic Review and Meta-Analysis. PLoS ONE 9: e98259.
71. Kenney-Herbert E, Al-Mayhani T, Piccirillo SGM, Fowler J, Spiteri I, et al. (2015) CD15 Expression Does Not Identify a Phenotypically or Genetically Distinct Glioblastoma Population. STEM CELLS Transl Med 4: 822-831.

72. Lazari D, Alexiou GA, Markopoulos GS, Vartholomatos E, Hodaj E, et al. (2017) N-(p-coumaroyl) serotonin inhibits glioblastoma cells growth through triggering S-phase arrest and apoptosis. J Neuro-Oncology 28: 373-381.
73. Kijewska M, Kocyk M, Kloss M, Stepniak K, Korwek Z, et al. (2016) The embryonic type of SPP1 transcriptional regulation is re-activated in glioblastoma. Oncotarget 8: 16340-16355.
74. Ranjan A, Srivastava SK (2017) Penfluridol suppresses glioblastoma tumor growth by Akt-mediated inhibition of GLI1. Oncotarget 8: 32960-32976.
75. Li W, Zhou Y, Zhang X, Yang Y, Dan S, et al. (2017) Dual inhibiting OCT4 and AKT potently suppresses the propagation of human cancer cells. Sci Rep 7: 46246.
76. Lin Y, Yang Y, Li W, Chen Q, Li J, et al. (2012) Reciprocal regulation of Akt and Oct4 promotes the self-renewal and survival of embryonal carcinoma cells. Mol Cell 48: 627-640.
77. Jones NM, Rowe MR, Shepherd PR, McConnell MJ (2016) Targeted inhibition of dominant PI3-kinase catalytic isoforms increase expression of stem cell genes in glioblastoma cancer stem cell models. Int J Oncol 49: 207-216.
78. Pratt D, Pittaluga S, Palisoc M, Fetsch P, Xi L, et al. (2017) Expression of CD70 (CD27L) Is Associated With Epithelioid and Sarcomatous Features in IDH-Wild-Type Glioblastoma. J Neuropathol Exp Neurol 76: 697-708.
79. Jin L, Ge H, Yang C, Long Y, Chang Y, et al. (2017) CD70 as a novel target of CAR-T-cell therapy for gliomas. J Clin Oncol 35: 148.
80. Ge H, Mu L, Jin L, Yang C, Chang YE, et al. (2017) Tumor associated CD70 expression is involved in promoting tumor migration and macrophage infiltration in GBM. Int J Cancer 141: 1434-1444.
81. Al Sayed MF, Jaeger-Ruckstuhl CA, Hilmenyuk T, Claus C, Bourquin J-P, et al. (2017) CD70 reverse signaling enhances NK cell function and immunosurveillance in CD27-expressing B-cell malignancies. Blood 130: 297-309.
82. Wang QJ, Yu Z, Hanada K-I, Patel K, Kleiner D, et al. (2016) Preclinical Evaluation of Chimeric Antigen Receptors Targeting CD70-Expressing Cancers. Clin. Cancer Res 23: 2267-2276.
83. Chahlavi (2005) Involving Gangliosides and CD70. Cancer Res 65: 5428-5438.
84. Pankratova S, Klingelhofer J, Dmytriyeva O, Owczarek S, Renziehausen A, et al. (2018) The S100A4 Protein Signals through the ErbB4 Receptor to Promote Neuronal Survival. Theranostics 8: 3977-3990.
85. Ambartsumian N, Klingelhöfer J, Grigorian M (2019) Calcium-Binding Proteins of the EF-Hand Superfamily. Humana Press; New York, NY, USA: 2019. The Multifaceted S100A4 Protein in Cancer and Inflammation 339-365.
86. Dmytriyeva O, Pankratova S, Owczarek S, Sonn K, Soroka V, et al. (2012) The metastasis-promoting S100A4 protein confers neuroprotection in brain injury. Nat Commun 3: 1197.
87. Chow K-H, Park HJ, George J, Yamamoto K, Gallup AD, et al. (2017) S100A4 Is a Biomarker and Regulator of Glioma Stem Cells That Is Critical for Mesenchymal Transition in Glioblastoma. Cancer Res 77: 5360-5373.
88. Liang J, Piao Y, Holmes L, Fuller GN, Henry V, et al. (2013) Neutrophils promote the malignant glioma phenotype through S100A4. Clin. Cancer Res 20: 187-198.
89. Xu Y, Wang J, Xu Y, Xiao H, Li J, et al. (2017) Screening critical genes associated with malignant glioma using bioinformatics analysis. Mol Med Rep 16: 6580-6589.
90. Aguilar-Morante D, Morales-Garcia JA, Santos Á, Perez-Castillo A (2015) CCAAT/Enhancer binding protein β induces motility and invasion of glioblastoma cells through transcriptional regulation of the calcium binding protein S100A4. Oncotarget 6: 4369-4384.
91. Wu W, Schecker J, Würstle S, Schneider F, Schönfelder M, et al. (2018) Aldehyde dehydrogenase 1A3 (ALDH1A3) is regulated by autophagy in human glioblastoma cells. Cancer Lett 417: 112-123.
92. Fedele M, Cerchia L, Pegoraro S, Sgarra R, Fedele M (2019) Proneural-Mesenchymal Transition: Phenotypic Plasticity to Acquire Multitherapy Resistance in Glioblastoma. Int J Mol Sci 20: 2746.
93. Cheng P, Wang J, Waghmare I, Sartini S, Coviello V, et al. (2016) FOXD1-ALDH1A3 Signaling Is a Determinant for the Self-Renewal and Tumorigenicity of Mesenchymal Glioma Stem Cells. Cancer Res 76: 7219-7230.
94. Zhang W, Liu Y, Hu H, Huang H, Bao Z, et al. (2015) ALDH1A3: A Marker of Mesenchymal Phenotype in Gliomas Associated with Cell Invasion. PLoS ONE10: e0142856.
95. Li M, Xiao A, Floyd D, Olmez I, Lee J, et al. (2017) CDK4/6 Inhibition Is More Active against the Glioblastoma Proneural Subtype. Oncotarget 8: 55319-55331.
96. Li G, Li Y, Liu X, Wang Z, Zhang C, et al. (2018) ALDH1A3 induces mesenchymal differentiation and serves as a predictor for survival in glioblastoma. Cell Death Dis 9: 1190.
97. Sullivan KE, Rojas K, Cerione RA, Nakano I, Wilson KF (2017) The stem cell/cancer stem cell marker ALDH1A3 regulates the expression of the survival factor tissue transglutaminase, in mesenchymal glioma stem cells. Oncotarget 8: 22325-22343.
98. Elsir T, Edqvist P-H, Carlsson J, Ribom D, Bergqvist M, et al. (2013) A study of embryonic stem cell-related proteins in human astrocytomas: Identification of Nanog as a predictor of survival. Int J Cancer 134: 1123-1131.
99. Mathieu J, Zhang Z, Zhou W, Wang AJ, Heddleston JM, et al. (2011) HIF induces human embryonic stem cell markers in cancer cells. Cancer Res 71: 4640-4652.
100. Jafri Malin Abdullah, Zulkifli Mustafa, Aini Ideris (2014) Newcastle Disease Virus Interaction in Targeted Therapy against Proliferation and Invasion Pathways of Glioblastoma Multiforme. BioMed Research International 11: 386470.