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The Challenges and the Promise of Molecular Targeted Therapy in Malignant Gliomas[1]

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Abstract

Malignant gliomas are the most common malignant primary brain tumors and one of the most challenging forms of cancers to treat. Despite advances in conventional treatment, the outcome for patients remains almost universally fatal. This poor prognosis is due to therapeutic resistance and tumor recurrence after surgical removal. However, over the past decade, molecular targeted therapy has held the promise of transforming the care of malignant glioma patients. Significant progress in understanding the molecular pathology of gliomagenesis and maintenance of the malignant phenotypes will open opportunities to rationally develop new molecular targeted therapy options. Recently, therapeutic strategies have focused on targeting pro-growth signaling mediated by receptor tyrosine kinase/RAS/phosphatidylinositol 3-kinase pathway, proangiogenic pathways, and several other vital intracellular signaling networks, such as proteasome and histone deacetylase. However, several factors such as cross-talk between the altered pathways, intratumoral molecular heterogeneity, and therapeutic resistance of glioma stem cells (GSCs) have limited the activity of single agents. Efforts are ongoing to study in depth the complex molecular biology of glioma, develop novel regimens targeting GSCs, and identify biomarkers to stratify patients with the individualized molecular targeted therapy. Here, we review the molecular alterations relevant to the pathology of malignant glioma, review current advances in clinical targeted trials, and discuss the challenges, controversies, and future directions of molecular targeted therapy.

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Introduction

Gliomas account for about 80% of primary malignant tumors in the central nervous system, and World Health Organization (WHO) classification divides gliomas into four grades with increasing degree of malignancy [1]. Each subgroup has a relatively specific prognosis that guides the clinical management; unfortunately, anaplastic gliomas (WHO III) and glioblastomas (GBMs, WHO IV) constitute the majority of gliomas and are essentially incurable.

Abbreviations: BBB, blood-brain barrier; CDK4, cyclin-dependent kinase 4; CDKN2A, cyclin-dependent kinase inhibitor 2A; c-KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; EGFR, epidermal growth factor receptor; FT, farnesyl transferase; FTI, FT inhibitor; GBMs, glioblastomas; GSCs, glioma stem cells; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; MGMT, O^6-methylguanine DNA methyltransferase; miRNAs, microRNAs; mTOR, mammalian target of rapamycin; OS, overall survival; PDGFR, PDGF receptor; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma susceptibility protein 1; RTK, receptor tyrosine kinase; SHH, sonic hedgehog; TCGA, The Cancer Genome Atlas; TKIs, receptor tyrosine kinase inhibitors; TMZ, temozolomide; VEGF, vascular endothelial growth factor

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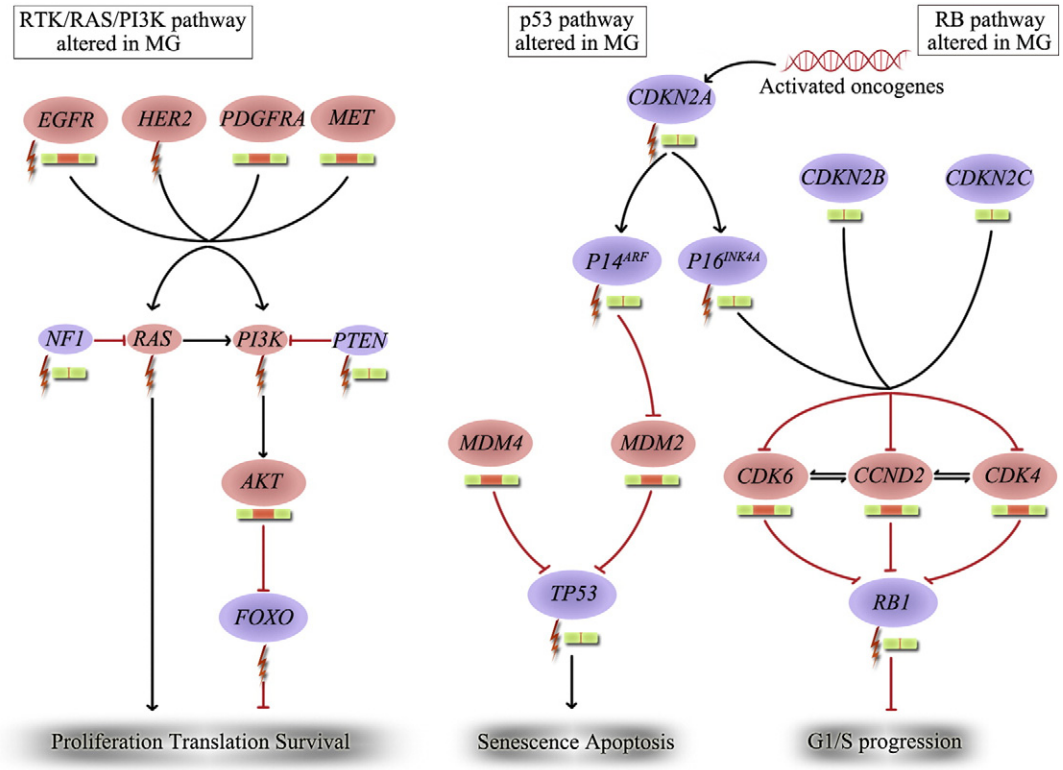

Figure 1. Three core signaling pathways altered in malignant gliomas. DNA alterations and copy number changes in the RTK/RAS/PI3K, RB, and p53 are shown. Moreover, activating genetic alterations are indicated in red, and inactivating genetic alterations are indicated in purple. In each pathway, the altered components and the type of alteration are indicated. The types of alteration are represented by different patterns as follows: represents mutation, represents amplification and represents homozygous deletion, while represents gene with normal copy number. MG indicates malignant glioma; HER, human epithelial receptor; MET, mesenchymal epithelial transition factor.

Currently, only surgical resection and adjuvant chemotherapy with temozolomide (TMZ) combined with radiotherapy are standard-of-care treatment strategies for this disease. However, the malignant behavior of these cancers with resistance to chemotherapy and radiation results in a high recurrence rate, and thus, patients with malignant glioma derive little benefit from standard treatments [2]. The disease ultimately follows a fatal course with the median survival of 12 to 15 months and 2 to 5 years for patients with GBM and anaplastic glioma, respectively [3].

To break through these challenges for malignant glioma therapy posed by limitations in the current therapeutic strategies, novel therapies such as molecular targeted therapy, immunotherapy, gene therapy, stem cell–based therapies, and nanotechnology have emerged from the interface between preclinical and clinical research [4]. Due to the success of molecular targeted therapy in several other cancer types such as non–small cell lung cancer [5], melanoma [6], and chronic myelogenous leukemia [7], this therapeutic strategy holds significant promise for the treatment of malignant glioma and has greatly advanced over the past decade, with such molecularly targeted therapeutics as bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), being granted approval by the US Food and Drug Administration for treating recurrent GBM in 2009 [8–10].

However, despite increasing radiographic response and progression-free survival (PFS), bevacizumab does not benefit overall survival (OS) in either recurrent GBM or newly diagnosed GBM [11–14]. Hence, with an increasing understanding of the molecular pathology of malignant glioma, novel signaling pathways driving gliomagenesis and progression that are candidates to become therapeutic targets and novel agents that may target relevant pathways more effectively are urgently needed. Herein, we set forth the rationales for targeting molecular pathways in malignant glioma, review current clinical trials for these tumors, and discuss the challenges, controversies, and future directions of molecular targeted therapy.

Multiple Core Signaling Pathways in Malignant Glioma

With high genetic and pathologic heterogeneity even in the same tumor sample, and low prevalence of each molecular abnormality, malignant gliomas are usually not defined by a single genetic mutation or molecular alteration. Thus, a "single gene–based" process of target identification and targeted therapy development is prohibitively difficult. It will be necessary to understand the pathways within which different genetic alterations function to drive gliomagenesis, progression, and treatment resistance and then focus our efforts in the development of a biologically meaningful classification scheme for treating these tumors.

Recently, The Cancer Genome Atlas (TCGA) research network identified three core signaling pathways underlying malignant glioma pathogenesis: receptor tyrosine kinase (RTK)/RAS/phosphatidylinositol 3-kinase (PI3K), p53, and retinoblastoma