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Targeting metabotropic glutamate receptors in the treatment of primary brain tumors

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In spite of the recent advancement in the molecular characterization of malignant gliomas and medulloblastomas, the treatment of primary brain tumors remains suboptimal. The use of small molecule inhibitors of intracellular signaling pathways, inhibitors of angiogenesis, and immunotherapic agents is limited by systemic adverse effects, limited brain penetration, and, in some cases, lack of efficacy. Thus, adjuvant chemo-therapy and radiotherapy still remain the gold standard in the treatment of grade-IV astrocytoma (glioblastoma multiforme) and medulloblastoma. We review evidence that supports the development of mGlu3 receptor antagonists as add-on drugs in the treatment of malignant gliomas. These drugs appear to display pleiotropic effect on tumor cells, affecting proliferation, differentiation, and response to chemotherapy. mGlu1 and mGlu4 receptors could also be targeted by potential anticancer agents in the treatment of malignant gliomas and medulloblastoma, but extensive research is required for target validation.

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Introduction

Metabotropic glutamate (mGlu) receptors are classically studied in nerve cells, where they modulate synaptic transmission and are considered as valuable drug targets for the treatment of neurologic and psychiatric disorders [1,2•,3••].

The seminal article by Suzy Chen and her Associates showing that one of the mGlu receptor subtypes (the mGlu1 receptor) promotes the development of melanoma when ectopically expressed in melanocytes [4] suggested the possibility that mGlu receptors may impact basic processes of cell biology, such as cell proliferation and differentiation, and opened an entirely new field: the study of mGlu receptors in cancer.

mGlu receptors form a family of eight subtypes divided into three groups on the basis of sequence homology, pharmacological profile, and transduction mechanisms. Group-I includes mGlu1 and mGlu5 subtypes, which are coupled to $G_{q/11}$. Their activation triggers the hydrolysis of phosphatidylinositol-4,5-bisphosphate, with ensuing formation of inositol-1,4,5-trisphosphate and diacylglycerol. Group-II (mGlu2 and mGlu-3), and group-III (mGlu4, mGlu-6, mGlu-7, and mGlu-8) subtypes are coupled to $G_{i/o}$, and their primary transduction mechanism is the inhibition of adenylyl cyclase. A large body of evidence suggests that activation of at least mGlu1, mGlu2, mGlu3, mGlu4, mGlu5 and mGlu7 may trigger the activity of intracellular signaling pathways, such as the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K) pathways, which are critically involved in tumor cell proliferation and survival [1].

The work by Suzy Chen's and Jarda Wroblewski's groups in the last years has substantially enriched our knowledge of how mGlu1 receptors influence the pathophysiology of melanomas in humans, paving the way to the use of drugs that restrain receptor activity in the experimental treatment of melanomas. A synopsis of this work can be found in an elegant review article, which also discusses the relationship between mGlu1 receptors and melanoma brain metastases [5••].

A growing body of evidence suggests a role for mGlu receptors in the development of many other types of cancer, including primary malignant brain tumors. This review article focuses on high-grade gliomas and medulloblastoma, which are the most aggressive malignant CNS tumors of the adult life and pediatric age, respectively.

Targeting mGlu3 and mGlu1 receptors in the treatment of malignant gliomas

Astrocytomas are classified into low- (I and II) and high-grade (III or IV or *glioblastoma multiforme*), based on the World Health Organization (WHO) grading system [6••].

Glioblastoma multiforme (GBM) is the most common and aggressive primary CNS tumor, with an incidence of 3.19/100.000 and a median age at onset of 64 years [7]. The prognosis is poor, with a rate of survival of 14–15 months from the time of presentation. Primary GBM is associated with epidermal-growth factor receptor (EGFR) gene mutation and amplification, loss of phosphate and tensin homologue (PTEN), overexpression of mouse double minute 2 (MDM2) and deletion of p16, while the secondary subtype often presents p53 and isocitrate dehydrogenase 1 (IDH1) mutations, platelet-derived growth factor receptor A (PDGFRA) and retinoblastoma (RB) genes overexpression, and loss of 19q [8]. These mutations lead to the activation of three main signaling pathways involving p53, RB, and phosphatidylinositol-3-kinase (PI3K). Based on molecular features, GBM can be divided into four subtypes: proneural, neural, classical and mesenchymal. Proneural subtype presents mainly IDH1 mutations, followed by CDK4, CDK6, PDGFRA, and MET alterations. The classical subtype is associated with EGFR amplification, PTEN and CDKN2A loss, and activation of Notch and sonic hedgehog signaling pathways. The mesenchymal subtype is associated with p53, NF1 and CDKN2A loss, while the specific gene signatures of the neural subtype have not been identified, as yet. These molecular hallmarks of GBM could help scientists to develop molecularly targeted therapies with a high degree of specificity for a particular tumor subtype [8].

Surgery is the primary therapeutic approach for newly diagnosed GBM patients and tumor resection is optimized by the use of fluorescent marking of tumor cells with 5-aminolaevulinic acid (5-ALA) [9]. Concomitant and adjuvant temozolomide (TMZ) chemotherapy in addition to radiotherapy is the current standard of care for patients with GBM up to age 70 [10].

Temozolomide is an oral alkylating agent, which acts mainly through methylation of DNA at the N7 or O6 positions on guanine residues. DNA mismatch repair system is not able to find a complementary base for methylated guanine, and this leads to a block in the cell cycle at G2-M transition phase, with resulting apoptosis [11]. Methylguanine-methyltransferase (MGMT) gene promoter methylation has been indicated as the strongest prognostic marker for outcomes in patients treated with temozolomide [12]. MGMT is a repair enzyme that promotes demethylation of O6-methylguanine and, therefore, restrains the therapeutic activity of temozolomide [11]. Drugs that inhibit MGMT activity or lower the expression of MGMT in GBM cells hold promise for the treatment of GBM when combined with temozolomide (see below).

Therapies targeting vascular endothelial growth factor (VEGF), such as the humanized monoclonal antibody, bevacizumab, show partial therapeutic effects in patients with GBM, by increasing progression-free survival and decreasing corticosteroid use, and has been approved by FDA as a second line therapy for GBM [13•]. Many other drugs, such as the EGF receptor inhibitor, nimotozumab [14], are under development for GBM treatment, which, however, remains largely suboptimal.

The intrinsic features of glioma stem cells (GSCs) highly contribute to the low susceptibility of GBM to the current therapies. GSCs display unlimited self-renewal potential and are resistant to chemo-therapy and radiotherapy through a number of innate and adaptive mechanisms. The exact percentage of GSCs present in GBM is difficult to determine because (i) not all GSCs express the stem cell marker, CD133; and, (ii) tumor cells bearing a stemness signature include not only *bona fide* GSCs but also their hierarchical progeny (i.e., transient amplifying and progenitor cells). The number of GSCs may vary in different GBM subtypes and even in different regions of the same tumor. It is extremely difficult to identify GSCs with intraoperatory fluorescent dyes as they specifically detect tumor cells with a high metabolic rate, whereas GSC metabolism is similar to that of surrounding neurons and astrocytes. To what extent tumor recurrence is supported by the local persistance of GSCs after surgical removal of the primary tumor or rather by different populations of GSCs that migrate from their site of origin is unknown. Of note, stem-like cells found in recurrent tumors display different markers, and are more aggressive than GSCs derived from the primary tumors [15–19]. Treatments that specifically target GSCs by either causing cell death or increasing their susceptibility to chemotherapy or radiotherapy are urgently needed.

A series of studies suggest that targeting metabotropic glutamate (mGlu) receptors in GSCs might represent a potential strategy for the treatment of GBM.

The study of mGlu receptors as candidate drug targets for malignant gliomas was inspired from the general belief that GSCs originate from transformation of neural stem cells (NSCs) of the subventricular zone (SVZ) [20]. NSCs and GSCs share different properties, such as expression of immature markers and regulation by growth factors and intracellular signaling pathways, such as bone morphogenetic proteins (BMPs) activating the phospho-Smad transduction cascade [20–22]. Moving from the evidence that NSCs express mGlu3 receptors [23,24], these receptors were also found in cells isolated from surgically removed GBM, in GSCs, and in glioma cell lines [25–27]. It has been reported that pharmacological activation of mGlu3 receptors supports proliferation and survival of GSCs, and that, in contrast, receptor blockade stimulates GSC differentiation into astrocytes [27,28]. The evidence that BMPs promote GSC differentiation into astrocytes [22] encouraged the search for a potential cross-talk between mGlu3 receptors and BMP receptors in GSCs.

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