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Review

Deregulated signalling networks in human brain tumours

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ABSTRACT

Despite the variety of modern therapies against human brain cancer, in its most aggressive form of glioblastoma multiforme (GBM) it is a still deadly disease with a median survival of approximately 1 year. Over the past 2 decades, molecular profiling of low- and high-grade malignant brain tumours has led to the identification and molecular characterisation of mechanisms leading to brain cancer development, maintenance and progression. Genetic alterations occurring during gliomagenesis lead to uncontrolled tumour growth stimulated by deregulated signal transduction pathways. The characterisation of hyperactivated signalling pathways has identified many potential molecular targets for therapeutic interference in human gliomas. Overexpressed or mutated and constitutively active kinases are attractive targets for low-molecular-weight inhibitors. Although the first attempts with mono-therapy using a single targeted kinase inhibitor were not satisfactory, recent studies based on the simultaneous targeting of several core hyperactivated pathways show great promise for the development of novel therapeutic approaches. This review focuses on genetic alterations leading to the activation of key deregulated pathways in human gliomas.

1. Introduction

The incidence of brain cancer tends to be highest in developed, industrialised countries. Primary brain tumours account for less than 2% of all human cancers but are very often associated with high mortality. Glioblastoma multiforme (GBM) is the most aggressive form of brain cancer, with a median survival of approximately 1 year. In the USA alone, 10,000 new cases are diagnosed each year at the rate of 3 per 100,000 persons [1,2]. Despite the available multimodality treatments, no cure or effective therapy for malignant gliomas has been developed to date. In a population-based study of glioblastomas in Switzerland, 17.7% of patients survived for 1 year, whereas only 3.3% of patients with newly diagnosed GBM survived for 2 years [3].

Current standard-of-care therapy for newly diagnosed malignant gliomas includes surgical resection, radiotherapy and temozolomide (TMZ), administered both during and after radiotherapy. Complete or nearly total surgical resection together with post-surgical radiation increases survival rate and, more recently, radiotherapy plus concomitant and adjuvant TMZ significantly improved survival of GBM patients without reduction in quality of life [4,5]. Temozolomide is an alkylating agent that crosses the blood–brain barrier; however, its activity can be antagonised by the DNA-repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT), which removes a methyl group from DNA and thus triggers a mechanism in GBM cells leading to TMZ resistance [6]. Interestingly, hypermethylation of the *MGMT* promoter occurs in multiple gliomas and, more important, its transcriptional silencing has been associated with significantly longer survival in cases of GBM and lower-grade gliomas treated by irradiation and alkylating agents, including TMZ [7,8]. Nevertheless, the survival rate for GBM remains very low and most patients develop fatal tumour recurrence or progression within 1 year of the treatment.

Thus, there is a clear need for a more efficient treatment that overcomes the resistance of malignant brain tumours to conventional therapies and significantly improves survival rate. The recent identification and characterisation of genetic and molecular mechanisms driving brain tumour development and progression has allowed

Abbreviations: GBM, glioblastoma multiforme; RTK, receptor tyrosine kinase; EGF (R), epidermal growth factor (receptor); PDGF(R), platelet-derived growth factor (receptor); VEGF(R), vascular endothelial growth factor (receptor); ERBB2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; MET, met proto-oncogene (hepatocyte growth factor receptor); PI3K, phosphoinositide-3-kinase; AKT, v-akt murine thymoma viral oncogene; TP53, tumour protein p53; RB1, retinoblastoma 1; CDK 4 (6), cyclin-dependent kinase 4 (6); CDKN2A (B) (C), cyclin-dependent kinase inhibitor 2A, (B) (C); CCND2, cyclin D2; MDM2, Mdm2 p53-binding protein homolog (mouse); MAPK, mitogen-activated protein kinase; RAF1, v-raf-1 murine leukemia viral oncogene homolog 1; ERK, mitogen-activated protein kinase 1; MEK, mitogen-activated protein kinase kinase; FOXO1, forkhead box O1; PTEN, phosphatase and tensin homolog; NF1, neurofibromin 1; MGMT, O-6-methylguanine-DNA methyltransferase; mTOR, mechanistic target of rapamycin; NFk-β, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; BAD, BCL2-associated agonist of cell death; BAX, BCL2-associated × protein; BCL2L12, BCL2-like 12 (proline rich); TGF-α, transforming growth factor, alpha; MCL1, myeloid cell leukemia sequence 1; S6K1, 40S ribosomal protein S6 kinase 1; eIF4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; HIF1, hypoxia-inducible factor 1; IDH1, isocitrate dehydrogenase 1

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the introduction of novel molecularly targeted therapies that represent promising avenues for therapeutic interference in human brain tumours.

2. Genetic alterations during glioma development and progression

To understand the mechanisms of gliomagenesis and the resistance to treatment, many studies have focused on gene expression profiling of brain tumours of different grades. According to the WHO scale, human brain tumours are graded as I to IV depending on malignancy as determined from tumour histopathologic features [9]. Grade I are benign tumours that can be cured by surgical resection. Low-grade (II) tumours show diffuse infiltration of surrounding tissue, whereas grade III tumours are characterised by increased proliferation and anaplasia and are more rapidly fatal. Grade IV tumours are the most aggressive and malignant, exhibiting vascular proliferation, necrosis and resistance to radiation and chemotherapy.

GBM is grade IV and such tumours arise by at least two different pathways: from a previous lower-grade astrocytoma (secondary GBM) or *de novo* from precursor cells (primary GBM) [10]. As shown in Fig. 1, these clinical variants seem to have different molecular profiles but are not clearly different in prognosis, with median survival of 12–15 months. Secondary GBMs are quite rare (ca. 10%) and tend to affect younger patients (below 45 years), whereas primary GBMs account for the great majority of GBM cases (90%) in older patients. Brain tumour profiling analysis together with other recent results [11–13] have revealed major molecular alterations during the genesis of human GBM. Deregulated core pathways promoting brain tumour development and progression include growth factor signalling via activation of receptor tyrosine kinases (RTK), phosphatidylinositol-3-OH kinase (PI3K) and AKT-signalling, as well as the inactivation of p53 and retinoblastoma tumour suppressor pathways.

2.1. Growth- and survival-promoting pathways

2.1.1. Receptor tyrosine kinases

Many hyperactivated cellular receptors in human gliomas belong to the RTK group. These kinases, together with deregulated non-receptor tyrosine kinases, activate several signalling pathways involved in cellular growth and survival as well as angiogenesis and invasion. Epidermal growth factor receptor (*EGFR*) gene amplification is very common in GBM, occurring in approximately 50% of cases, and many GBM patients also express a constitutively active, truncated isoform of EGFR lacking the extracellular binding domain [14]. Approximately 20–30% of GBM patients express a mutant EGFR lacking exons 2–7 (EGFRvIII), which results in ligand-independent tyrosine kinase activity that stimulates downstream survival and growth pathways [15,16]. Moreover, gliomas may release the EGFR ligands EGF and TGF-alpha, thus supporting EGFR activation and cellular growth in an autocrine manner [17].

High-grade malignant brain tumours show enhanced resistance to death- and apoptosis-stimulating agents. Hyperactivated RTKs and their downstream PI3K/AKT pathway not only stimulate growth but also contribute to an increase in anti-apoptotic features of glioma cells by various mechanisms. The reported correlation between anti-apoptotic protein BCL-2 and tumour grade, where it is more abundant in grade III/IV than in grade I/II gliomas, and the association of MCL-1 expression with early tumour recurrence and shorter survival of glioma patients, clearly indicate that cancer cells acquire resistance to apoptosis via overexpression of anti-apoptotic proteins during gliomagenesis [18,19]. Indeed, upregulation of anti-apoptotic protein Bcl-xL was shown to be induced by hyperactivated EGFR pathways in human glioma cells and this upregulation conferred resistance to the chemotherapeutic agent cisplatin [20].

Other relevant induction of RTKs in malignant gliomas includes overexpressed platelet-derived growth factor receptor (PDGFR) and its ligands (PDGFs) in lower-grade astrocytomas. In addition, PDGFs are also highly expressed in high-grade brain tumours as well as in proliferating endothelial cells. Thus the activation of PDGFR in GBM can occur by both autocrine and paracrine mechanisms [21–23]. More recently, The Cancer Genome Atlas (TCGA) pilot project [12] reported major cancer-causing genome alterations by integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 GBMs. The analysed cohort represented predominantly primary glioblastomas, although a small number of progressive secondary GBM were included. In addition to the especially well-studied EGFR and PDGFR activation, the study reported the genetic

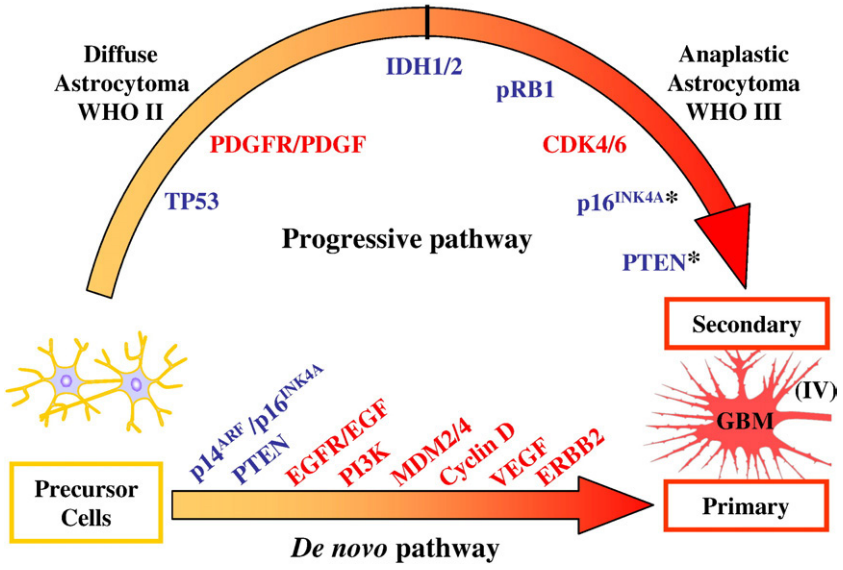

Fig. 1. Major genetic alterations leading to glioblastoma development. Primary and secondary glioblastoma multiforme (GBM) develop from precursor cells, including astrocytes or glial precursors, as a result of *de novo* pathway or progressive pathway from low-grade astrocytomas (diffuse WHO grade II and anaplastic with grade III), respectively. Although primary and secondary GBM are classified as grade IV and have similar patient prognoses, many profiling analyses have revealed genetic and molecular differences between these two types of tumours. Genes that are inactivated via mutation or deletion are depicted in blue, and genes that are induced and hyperactivated during gliomagenesis by various mechanisms, including gene amplification, overexpression or mutation, in red. *Less frequent inactivation in secondary as compared to primary GBM.