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Review Article

Animal Model for Glioma: A Brief Overview

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Abstract

Glioblastoma remains the most aggressive malignancies of the brain with dismal prognosis. Typically, it is pathologically characterized by nuclear polymorphism, cellular atypia, necrosis and aggravated angiogenesis. Recently, the 2016 WHO classification, has however given impact on profiling of molecular markers as IDH, EGFR for better prognostic assessment. Animal model are needed to recapitulate the pathology of naturally growing tumors to develop and update the therapeutic regime. Present review provides a glimpse of molecular pathology of glial tumors and the existing animal models being used for glioma research.

Keywords

Glioblastoma; Murine model; WHO; IDH

Introduction

The term glioma covers the most common malignancy of the central nervous system (CNS). Depending on the cell of origin, it can be an astrocytoma (originated from astrocytes), oligodendroglioma (originated from oligodendrocytes) or ependymoma (originated from the ependymal cells) [1]. It is estimated that 30000 peoples are diagnosed with glioblastoma per year in USA. In India, we have previously reported that patients succumb to glioblastoma at earlier age than western population. Overall, males were overall found to more frequent than females. Headache and seizures were most frequently observed in glioblastoma patients [1,2]. Among the risk factors, neurofibromatosis 1 and 2 have increased risk of glioma or astrocytoma development. Among the environmental factors, radiation, occupational exposure, electromagnetic fields, cellular phones, brain trauma are widely cited [3,4].

World Health Organization (WHO) in 2007 has classified gliomas on the basis of cell of origin and the histopathological appearance. Glioblastoma is the most aggressive glioma [5]. Recently, WHO 2016 classification uses the molecular markers as IDH, 1p/11q mutations to designate the prognostic outcomes [6]. The new classification has better suited to grasp clinical trials more safely. Further, it forces neurosurgeons to remain updated with the recent concepts and information [7]. The standard care for the glioblastoma patients consists of surgical resection followed by radio and/or chemotherapy. However, the present therapeutic regime has not influenced the median survival age and quality life of glioblastoma patients [8-10].

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The glioblastoma can be either a primary glioblastoma or a secondary glioblastoma. The primary glioblastoma is more frequent and aggressive. It is known to arise without any previous history of low grade tumors and effects the elderly population to the most (dominantly men). The secondary glioblastoma, on contrary, is reported to arise from diffuse astrocytoma (GII astrocytoma) or anaplastic astrocytoma (GIII astrocytoma) over the time scale of 5-10 years. The secondary glioblastoma is often found in younger population with median age of 45 years [11,12].

Molecular pathology of glial tumors

The recent 2016 WHO classification has provided the significance of molecular markers in providing the near accurate prognostic information [6]. Mutations in the gene encoding enzyme isocitrate dehydrogenase (IDH) are observed in nearly 80% WHO II and III astrocytoma and in 12% of glioblastoma [13,14]. The mutations are most commonly observed in cytosolic IDH1 and known to alter the epigenomics profile. The IDH mutant gliomas are known to alter the DNA methylation profile in diffuse gliomas [15]. IDH1 or IDH2 mutations are known to co-occur with 1p/11q codeletions in oligodendrogliomas. The 1p/11q codeletion is generally viewed as hallmark of oligodendroglial tumors and associated with the better prognosis in clinical cases. The primary glioblastomas are generally found to be IDH wild type while the secondary glioblastomas as IDH mutant. It is still remains enigmatic how these mutations affect the biological behavior of the tumors [16]. It is also reported that the IDH mutations corresponds to better overall and progression free survival [17]. Mutations in the promoter of TERT (telomerase reverse transcriptase) are most frequently noted [18]. EGFR overexpression is known to promote invasive potential in glioma and tumor progression [19]. O(6)-methylguanine-DNA methyltransferase (MGMT) is a well-studied gene in gliomas. The gene encodes a repair enzyme that counteracts the harmful effects of alkylating agent as temozolomide. Its activity promotes double strand breaks and base impairing thus promoting apoptosis and cell death [20]. Further, MGMT promoter methylation is reported to be associated with longer overall survival in glioblastoma patients treated with alkylating agents [21]. Glial tumors are noted with mutations in the cellular signaling pathways as PI3K-AKT pathway, cell cycle control pathways that promotes the entry of cells in G1 to S phase. The PI3K-AKT pathway is reported to be often overactive on account of activating mutations of the genes involved as receptor tyrosine kinase (RTK) or PTEN which is a tumor suppressor gene and repressor of the pathway. Similarly, p53 is also noted with the inactivating mutations which facilitates the unrestricted entry of cancer cells in G1-S phase. Mutations in the genes controlling cell cycle pathways as cyclin D1, cyclin dependent kinase 4 (CDK4) brings about the controlled progression in cell cycle [22-24]. EGFR and PDGFRA are most commonly reported to be amplified in glial tumors and contribute to its progression. EGFR and PDGFRA amplification events are postulated to happen together common progenitor cell. Efforts are being under way to target the pathways associated with the two proteins together for better efficacy [25,26]. A classification scheme has been proposed based on the coexpression of EGFR and PDGFRA modules. It assigns the diffuse gliomas to subtypes based on the coexpression of transcriptomic and genomic components. This scheme is supposed to provide the molecular framework for

accurate therapeutics [27]. The details of the genes involved in glioma pathogenesis are indexed in Table 1.

Present therapeutic regime for glial tumors

Low grade glioma (LGG) is known to display heterogeneous pathology and the patients may survive ranging from 2-20 years [28]. Apparently low grade glioma are slow growing in nature and capable for progressing into malignant forms [29]. Age factor is reported to influence the aggressive radiation therapy for LGG on account of the possible risk of radiation. However, for older patients, immediate postoperative radiation is preferred. Temozolomide is known to give the response ranging from 20-52% [30,31]. The addition of procarbazine, lomustine and vincristine (PCV) therapy is shown to adjuvant radiiation in patients (>40) provided the survival advantage [32]. High grade glioma (HGG) are generally treated with the surgical resection followd by the radiation therapy. This, however, did not influence the overall 5 year survival of patients which was noted to be 2-3% [33]. Concurrent and adjuvant therapy of temozolomide along with the RT is shown to benefit the overall survival of gliobalstoma pateints tan the RT alone. The MGMT methylation has been viewed to promote the overall survival in responce to temozolomide [34,35]. EGFR is known to be overexpressed in glioblastoma and promotes the tumor survival. Tyrosine kinase inhibitors as gefitinib and erlotinib are reported to inactivate the associated downstream signalling in recurent glioblastomas [36]. The clinical trials however show that there is no significant relief to the patients of recurrent glioblastoma [37,38]. Bevacizumab, a humanazied monoclonal antibody specifically targets VEGF and blocks the downstream signalling and improves the progression free survival. This drug, however has been shown to be associated with complications as gastrointestinal perforation and intracranial hemorrhage [39,40]. Along with the other noted inhibitors, Cilengitide is known to target the integrin and hamper angiogenesis and migration [41]. The inhibitors of signaling downstream to growth factor receptor includes temsirolimus as inhibitor of mTOR associated signaling [42], Tipifarnib, Lonafarnib as inhibitor of RAF-MEK-ERK pathway [43,44]. Other inhibitors has been listed in Table 2.

Intratumoral heterogeneity has been conformed in same set of tumor biopsies [45]. It is also reported that glioma tumor tissues contains the subpopulation of cells with mutually exclusive overexpression of PDGFRA and EGFR [46] making them resistant to single course of treatment. Despite of the available wealth of information, there is no significant change in the overall quality life of patients diagnosed with glioblastoma. Therefore, it is necessary to see the molecular profile of tumors in preclinical as well as in clinical models to enhance the therapeutic efficacy.

Glioma cell lines

Glioma cell lines derived from human counterparts are widely used as pre-clinical model on account that it shows much of the genetic similarity. The most widely used human cell lines include U87, LN18 and U251 [47]. The ideal prerequisites pre-clinical model includes similar genetic make-up and heterogeneity as well should imitate the tumor microenvironment [48].

Mouse model

Glioma model induced by Ethyl-nitrosourea (ENU) injections: This model was developed in late 1970s and is based on the intravenous injections by ENU. The exposure of ENU to pregnant rats is generally given on 18th day of gestation. The tumours are formed due to errors in DNA repair mechanisms. The most probably formation of brain tumors could be the absence of active DNA repair machinery in brain compared to other tissues. This model can help to imitate the tumors in humans which are induced by the key driver mutations as p53, genetic instability or the accumulation of mutations in genes vital for the cell cycle progression. The ENU induced model represents the human glioma in few aspects as the tumor microenvironment, active immune system and the intact blood-brain –barrier. The limitations may include poor reproducibility, high requirement of time and cost in generating the model [49].

Transgenic model in mouse: The most classic example of this is the Cre-Lox model. Here, the LoxP transgenic mice overexpressing the oncogene as Ras and conditionally lacking the tumor suppressor gene as p53. The Cre recombinase is generally put under the glial cell specific promoter as GFAP. This type of model need the knowledge of driver mutations to design the Cre-Lox system. This type of model is used to investigate the efficacy of candidate drug compounds in predefined genetic make-up. These, however, lacks the tumor heterogeneity generally observed in human tumors [50].

Table 1: Most commonly reported genes as therapeutic targets in glioma.

Sr. no	Gene name	Function in glioma	Ref.				
1.	IDH	Alters the methylation pattern, associated with better overall and progression free survival	[15,17]				
2.	EGFR	Promotes invasive proprieties and glioma progression	[19]				
3.	MGMT	Associated with longer overall Survival in patients treated with alkylating agents	[21]				
4.	1p/11q	Co-deletion is viewed as marker of better prognosis in oligodendroglial tumors	[16]				
5.	TERT	Promotes telomerase reverse transcriptase activity	[18]				
6.	PTEN,p53	Tumors suppressor genes, halts the entry of cancer cells in G1-S phase	[21-24]				
7.	Growth factors (EGFR, PDGFRA)	Promotes cellular proliferation, confers therapy resistance	[25]				

Table 2: Most common!	v used drugs as	chemotherapeutic	agents in gliom
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Sr. no	Name of Drug	Mechanism of action/ target gene	Ref.
1	Temozolomide	Alkylating agent	[30,31]
2	Procarbazine, Lomustine and Vincistine (PCV)	Alkylating agent	[32]
3	Gefitinib and Erlotinib	EGFR inhibitor	[36]
4	Bevacizumab	Angiogenesis inhibitor, targets VEGF	[39,40]
5	Cilengitide	Angiogenesis inhibitor, targets integrin	[41]
6	Temsirolimus	mTOR inhibitor	[42]
7	Tipifarnib, Lonafarnib	Inhibitor of RAF-MEK-ERK pathway	[43,44]

Murine allograft model: The allograft model is generated by injecting the glioma cell lines of murine origin (as C6) intracranially in wistar rats or in C57BL/6 mice. The advantage of the model is that the cell lines can be implanted orthotopically in animals with active immune system. Allogeneic immune response is observed in wistar rats with reduced tumor growth [51]. The invasive tumors developed after intracerebral implantation of the cell line are generally invasive and used to investigate the effect of targeted therapies.

The drawbacks of mouse model may include few as it may not completely recapitulate the pathology of tumors originate in humans. Secondly, the course of targeted monoclonal antibodies may not imitate on account of difference in complete set of immunological reactions between human and mouse/rats.

Human glioma model

Cell line and neurosphere culture: As noted earlier, U87 and U251 cells are the most widely used ones for pre-clinical research. Irrespective of the time and accumulated genetic alterations over the time, the original genetic aberrations are still retained in these cell lines and are helpful to study the detailed mechanism of associated signaling for therapeutic implications [52]. However, the presence of serum in the culture medium causes genetic drift and thus affecting the reproducibility. Considering this limitation, the neurosphere cultures are practiced. Surgically resected glioma tumor tissues are grown in culture medium containing basic fibroblast growth factor (bFGF), epidermal growth factor and neuronal viability supplement B27. IDH mutations are known to affect the generation of neurospheres. Low grade glioma with mutated IDH are known to be difficult for cultures [53]. These spheroid cultures also postulated to express the glioma stem, cell markers but unstable under the influence of growth factors in the culture medium. The underlying mechanisms however are unclear.

Orthotropic glioma models: In orthotopic patient derived xenograft model, the tumor tissue is directly implanted in the brain of immunodefecient animas. One of the drawback of the model includes the presence of active immune system and the tumor microenvironment in animal. Further, there is no heterogeneity in the planted tumors as the mutated part of tumor grows more aggressively than the rest of tumor part. Moreover, there may not be pathological resemblance with the original tumor [54]. Attempts are being driven to reconstitute the immune system in animals to resemble the immunology of originally occurring tumors for better therapeutic targeting.

Summary

Glioblastoma has remained a disease with dismal clinical outcome irrespective of the advanced therapeutic regime. Animal models developed for glioma research have facilitated the understanding of the disease for therapeutic intervention. The chief obstacles fully recapitulate the biology and the heterogeneity of original tumors are their immediate microenvironment, active blood-brain barrier, the unique set of driving mutations and the immune system of animals. So far the ideal model that could mitigate the inherent limitations do not exist. The choice of existing animal model depends on the set of questions one is palling to address while considering the strength and the flaws of the particular model.

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Ethical Approval and Informed Consent

Not applicable.

Conflict of Interest

None References

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