

A comprehensive review of available omics data resources and molecular profiling for precision glioma studies (Review)

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Received April 4, 2018; Accepted November 11, 2018

DOI: 10.3892/br.2018.1168

Abstract. Gliomas are the most common and lethal type of primary malignant central nervous system tumors, with an extremely poor prognosis. The latest progression in the technological development of sequencing/microarray and bioinformatics has provided insights into the glioma genome. These technologies have generated large amounts of easily accessible biological omics data, providing an unprecedented opportunity to study glioma formation. According to the 2016 WHO organization classification of brain tumors, gliomas are currently diagnosed with respect to morphological and molecular tumor alterations, especially for isocitrate dehydrogenase and 1p/19q codeletions. In the present study, the comprehensive molecular profiling and available omics data resources for malignant gliomas were reviewed for novel insights into the biology and classification of these tumors. These molecular profiling resources may be useful for improving the understanding of malignant gliomas, and to accelerate the clinical, experimental and epidemiological studies that may lead to improvements in the lives of patients with glioma.

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1. Introduction

Gliomas are the most common primary and among the most fatal types of malignant brain tumors, with an annual incidence of 5.26 per 100,000 population and an overall 17,000 incident diagnoses per year in the United States; and the number of patients is expected to increase with increases in population age (1-3). Based on the histopathological classification of the 2016 WHO central nervous system tumors, gliomas are diagnosed from lowest to highest grades: Grade I angiocentric gliomas; grade II oligodendrogliomas [isocitrate dehydrogenase (IDH)-mutant and 1p/19q-codeleted] and diffuse astrocytomas (IDH-mutant); grade III anaplastic oligodendrogliomas (IDH-mutant and 1p/19q-codeleted) and anaplastic astrocytomas (IDH-mutant); and finally grade IV glioblastomas (GBM) and diffuse midline gliomas (H3K27m-mutant) (4). Although histopathological grades remain useful, the prognoses of patients with glioma are more closely associated with molecular alterations compared with grades (5,6). Notably, patients with glioma are typically associated with heterogeneous tumor morphologies and variable prognoses. Despite therapeutic advances, gliomas remain incurable, with the most aggressive forms resulting in mortality within months (7). Therefore, there is an urgent requirement to increase the understanding of the etiology, pathology and taxonomy of glioma, to improve the selection of treatment options for patients and to develop novel therapeutic strategies.

High-throughput sequencing and microarray technologies, for example whole-genome sequencing and RNA sequencing, provide an opportunity to examine the broad range of genomic information at an unprecedented high resolution. Previous technological advances (e.g., RNA-Seq, microarray) and the exponential decrease in the cost of genome sequencing and microarray detection have made biological data resources increasingly accessible (8-10). In previous decades, molecular biomarker-based diagnostics with glioma have resulted in a change in the traditional pathological classification methods of glioma, resulting in more reproducible and precise clinically distinct subtypes (11-15). At present, IDH mutations and codeletion of chromosome 1p and 19q arms, as a molecular signature, are now included in standard glioma diagnosis and classification methods (4,16-18). In addition, the roles of several key genes have been described, including telomerase

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Key words: glioma, omics data, molecular profiling

reverse transcriptase (TERT) (19,20), phosphatase and tensin homolog (PTEN) (21), alpha thalassemia/mental retardation syndrome X-linked (ATRX) (22), B-Raf proto-oncogene, serine/threonine kinase (23) and O-6-methylguanine DNA methyltransferase (MGMT) (24). In light of these data, the molecular genetic signatures should be valuable in the diagnostic evaluation or treatment strategies for glioma (25).

Large population-based data sources are required to provide accurate descriptions of the mechanism of glioma. Previous data collection and integrative data analyses, for example, The Cancer Genome Atlas (<http://cancergenome.nih.gov/>) or Chinese Glioma Genome Atlas (<http://cgga.org.cn>), have revealed the genomic landscape of either low-grade or high-grade gliomas. In the present review, the available data resources and the molecular biomarkers from precision glioma studies were summarized. The aim of the present study was to provide a wide overview of existing data and recent molecular profiling, which may improve the current knowledge base in this field, and thereby assist in generating novel pathological classification categories, diagnostic methods, and novel therapeutic approaches to accelerate studies into the causes and control of glioma.

2. Available glioma data resources

Previously described high-throughput technologies have provided the opportunity for the extensive characterization of genomic statuses, including, but not limited to, genetic alterations, methylation modification and gene expression regulation (26,27). Over the previous decade, several genome projects were initiated, accelerating the comprehensive understanding of the genetics of glioma (Table I). Using innovative genome analysis technologies may assist in generating novel glioma therapies, diagnostic methods and preventive strategies (12,28,29). Therefore, the present study reviewed currently available glioma data resource in this community.

The Cancer Genome Atlas (TCGA). In 2005, the National Institute of Health and National Human Genome Research Institute began the TCGA project to generate comprehensive multi-dimensional maps of the key genomic alternations that promote malignant transformation. TCGA pilot project aimed to depict the molecular characteristics of multiple ‘omics’ in human cancer and to generate a data resource for the scientific community. As the most common and lethal intracranial tumor, glioma was the first type of cancer studied by TCGA Research Network. At present, it contains data from GBM and lower grade gliomas from multiple platforms, including copy number (1,090 samples), DNA methylation (936 samples), RNA-seq profiling (676 samples), mRNA microarray profiling (567 samples), miRNA microarray profiling (565 samples) data recorded in the Broad FireBrowse database (<http://firebrowse.org/>). Integrative analysis of DNA copy number, gene expression and DNA methylation data in 206 GBMs revealed that several key genes [including erb-B2 receptor tyrosine kinase 2, neurofibromin 1 (NF1), tumor protein p53 (TP53), phosphoinositide 3-kinase regulatory subunit 1 and cyclin dependent kinase inhibitor 2A/B (CDKN2A/B)] and signaling pathways (including receptor tyrosine kinase/Ras/phosphoinositide 3-kinase, TP53 and CDKN2A) were identified

to be frequently mutated in human GBMs, demonstrating that these data may improve the understanding of the molecular basis of cancer (30). In addition, a robust gene expression-based molecular classification of GBMs into the proneural, neural, classical and mesenchymal subtypes described by TCGA network provided evidence to support the requirement for targeted therapeutics (13). This study unifies genomic and transcriptome dimensions for molecular GBM stratification by abnormalities in platelet derived growth factor receptor alpha (PDGFRA), isocitrate dehydrogenase (NADP(+))1, cytosolic (IDH1), epidermal growth factor receptor (EGFR) and NF1 genes, which may provide important insight for future clinical application. Previously, Brennan *et al* (28) performed the largest multi-platform genomic analysis to define the critical genes associated with gliomas by using 1,122 all-grade gliomas from TCGA. In this study, they identified six methylation groups and four RNA expression groups, calculated molecular correlations and provided understanding of the malignant progression of gliomas. The results of the whole-genome sequencing revealed that ATRX but not TERT promoter mutations were associated with increased telomere length, indicating an alternative mechanism for telomeres lengthening. Notably, a group of IDH mutant glioma was associated with DNA demethylation and relatively poor survival; a subtype of IDH-wild glioma exhibited molecular similarity to pilocytic astrocytoma and favorable outcomes. This multi-omics glioma analysis provided novel insights into genomic alternations, emphasized the relevance of DNA methylation profiles for clinical classification, and associated somatic alterations involved in telomere maintenance.

At present, several exploratory analysis tools and databases have also been developed based on TCGA datasets. The cBio Cancer Genomics Portal (cBioPortal; <http://cbioportal.org>), an open-access and open-source resource, was developed as an interactive exploration of cancer genomics datasets and an intuitive method of presenting data, including the capacity to quickly view genomic alterations of genes or pathways of interest across a set of patients, and performing survival and biological network analysis (31,32). The portal currently stores DNA copy number variants, methylation, mRNA and microRNA expression, protein and clinical data. In addition, these TCGA datasets may be also easily and directly downloaded via the Broad FireBrowse website, which is updated regularly. These tools provide rapid, intuitive access to cancer genomics profiling and matched clinical data, and allows the translation of these valuable data into biological insights and clinical applications. To investigate the biological nature of TCGA long non-coding RNAs (lncRNAs), Cerami *et al* (31) and Gao *et al* (32) developed the TANRIC and Co-LncRNA databases, respectively, which facilitated the study of the biological functions of lncRNA and their clinical applications.

Chinese Glioma Genome Atlas (CGGA). The CGGA project (<http://cgga.org.cn>) is hosted and supported by the Beijing Neurosurgical Institute and the Chinese Glioma Cooperative Group Research Network. This project is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of glioma, particularly in secondary GBMs through the application of high-throughput biotechnologies and bioinformatics. The project aims to catalogue and identify

Table I. Summary of available omics glioma data reviewed in the present study.

Source	Platform	Samples (n)	Histology	Grade	Survival	Reference
TCGA	Illumina Human Methylation 27K/450K	936	Y	Y	Y	http://firebrowse.org
	RNA-seq Hiseq	676	Y	Y	Y	http://firebrowse.org
	mRNA Agilent-4502A/Affymetrix UG133A	567	Y	Y	Y	http://firebrowse.org
	Human miRNA 8x15K Microarray	565	Y	Y	Y	http://firebrowse.org
CGGA	Illumina Human Methylation 27K	151	Y	Y	Y	http://cgga.org.cn
	RNA-seq Hiseq 2000	325	Y	Y	Y	http://cgga.org.cn
	mRNA Agilent Whole Human Genome	301	Y	Y	Y	http://cgga.org.cn
	miRNA Human v2.0 Expression BeadChip	198	Y	Y	Y	http://cgga.org.cn
Madhavan <i>et al</i>	mRNA Affymetrix HG-UG133 Plus 2.0	566	Y	Y	Y	(35)
Ballester <i>et al</i>	Genomic Variants-next-generation sequencing	342	Y	Y	N	(36)
Gravendeel <i>et al</i>	mRNA Affymetrix HG-UG133 Plus 2.0	276	Y	Y	Y	(5)
Lee <i>et al</i>	mRNA Affymetrix HG-U133A	191	N	N	N	(53)
Phillips <i>et al</i>	mRNA Affymetrix HG-U133A	100	Y	Y	Y	(54)

TCGA, The Cancer Genome Atlas; CGGA, Chinese Glioma Genome Atlas; Y, yes; N, no.

Table II. Summary of key gene alternations in gliomas.

Histology	Molecular abnormalities	WHO grade
Oligodendroglioma	IDH-mutant & 1p/19q-codeleted	WHO II
Astrocytoma (IDH-mutant)	TERT promoter-wildtype IDH-mutant	WHO II
Astrocytoma (IDH-wildtype)	IDH-wildtype	WHO II
Anaplastic astrocytoma (IDH-mutant)	IDH-mutant	WHO III
Anaplastic astrocytoma (IDH-wildtype)	IDH-wildtype	WHO III
GBM (IDH-wildtype)	TERT promoter-mutant IDH-wildtype	WHO IV
GBM (IDH-mutant)	TERT promoter-mutant IDH-mutant	WHO IV
GBM (F3-T3+)	FGFR3-TACC3 gene fusion	WHO IV
Secondary GBM (ZM+)	PTPRZ1-MET gene fusion	WHO IV

WHO, World Health Organization; GMB, glioblastoma; IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; FGFR, fibroblast growth factor receptor; TACC, transforming acidic coiled-coil containing protein; PTPRZ1, protein tyrosine phosphatase receptor type Z1; MET, MET proto-oncogene, receptor tyrosine kinase; F3-T3, FGFR3-TACC3; ZM, PTPRZ1-MET fusion.

major genomic alternations that drive glioma progression, and to provide a detailed genomic characterization of a large cohort of Chinese gliomas.

To share this resource, the CGGA portal was established as an open-access platform for the interactive exploration of multidimensional glioma genomics datasets. At present, it provides access to DNA methylation microarray (149 samples), mRNA microarray (305 samples) and sequencing (325 samples), microRNA microarray (198 samples) data

and matched clinical data. Using the gene expression profile from an Agilent microarray of 225 samples from the CGGA, consensus average linkage clustering identified three major subgroups (G1, G2 and G3) (33). The G1 subtype demonstrated improved clinical outcome, young age and a high frequency of IDH1 mutation. The G3 subtype was characterized by poorer clinical outcome, older age and low frequency of IDH1 mutation. The parameters for clinical outcome, age and IDH1 mutation in the G2 subgroup were in between the

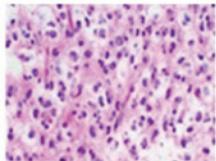
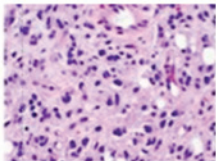
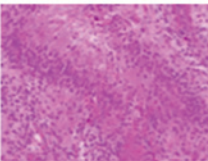
Pathology			
WHO grade	WHO II	WHO III	WHO IV
Histology	Oligo	Astrocytoma	GBM
Molecular Abnormalities	IDH1/2 mutant TERT promoter mutant 1p/19q codeleted	IDH1/2 mutant TERT promoter-wildtype ATRX mutant or deletion TP53 mutant	TERT promoter mutant IDH1/2-wildtype EGFR amplification

Figure 1. Traditional molecular pathology of glioma. WHO, World Health Organization; GMB, glioblastoma; IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; ATRX, α thalassemia/mental retardation syndrome X-linked; TP53, tumor protein p53; EGFR, epidermal growth factor receptor.

values for the G1 and G3 subtypes. Combining mutation data of the TERT promoter and IDH from 377 CGGA grade II/III glioma samples, Brat *et al* (12) performed a molecular classification of glioma into IDH-mutation/TERTp-mutation, IDH-mutation only, TERTp-mutation only and IDH-wild type/TERT promoter-wild type groups. Patients with only TERTp-mut genotypes exhibited the poorest prognoses, while patients with an IDH mutation alone demonstrated more favorable prognoses. This study suggested that combining mutation data from the TERT promoter and IDH genes created a novel method of defining glioma subgroups to supplement the traditional histopathological criteria for disease diagnosis. To facilitate an increased use of these RNA sequencing data from the CGGA project, a free, web accessible and use-friendly database was also constructed (GLIOMASdb; <http://cgga.org.cn:9091/gliomasdb/>) (34). The GLIOMASdb currently provides data available to download and analysis of gene patterns in the malignant progression of gliomas.

Other datasets. The rapid expansion of integrated multi-omics, bioinformatics analyses and clinical translation has markedly altered the understanding of glioma. Over the previous decade, several other glioma genome projects have been undertaken.

The REpository of Molecular BRAin Neoplasia DaTa (REMBRANDT), a cancer clinical genomics database and an online mining and analysis platform, aimed to improve understanding of glioma by effectively combining clinical information and genomic characteristics (35). To date, REMBRANDT includes 874 glioma specimens comprising ~566 gene expression arrays, 834 DNA copy number arrays and 13,472 clinical data, which may be used as an independent dataset for glioma research.

To improve glioma stratification standards, Gravendeel *et al* (5) performed gene expression profiling (Affymetrix HU133 Plus 2.0, $n=276$) from patients with glioma (GSE16011). In this study, seven distinct molecular subgroups were identified and correlated with survival. These contained two subgroups with favorable prognosis (median survival >4.7 years), two intermediate prognostic subtypes

(median survival of 1-4 years), two with poor prognosis (median survival of <1 year) and one control group. This result was validated by 5 other independent datasets, supporting this evidence that gene expression profiling may be an effective method to classify gliomas, and that this molecular classification may assist to diagnose and guide clinical decision making.

In addition, Ballester *et al* (36) performed a retrospective analysis of sequencing results of 381 primary gliomas. These cases, including GBM ($n=227$), anaplastic astrocytomas ($n=46$), diffuse astrocytoma ($n=37$), anaplastic oligodendrogliomas ($n=21$) and oligodendrogliomas ($n=11$), were used to identify mutations and amplifications in cancer-associated genes using a validated, commercially-available panel. The results revealed that the most commonly mutated genes included TP53 (37.2%), IDH1 (29.4%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA; 8%), PTEN (8%) and EGFR (7.5%). In addition, 23% cases (88/381) exhibited genomic amplification in at least 1 cancer-associated gene in the specific panel. The most common genes that indicated evidence of amplification included EGFR (18.0%), PDGFRA (2.5%) and KIT proto-oncogene receptor tyrosine kinase (1.8%). This study demonstrated the utility of next-generation sequencing for the identification of genetic alterations in brain tumors in the clinical setting.

3. Molecular profiling as a precise clinical tool

At present, treatment decisions in patients with glioma primarily depend on histological classification and clinical parameters. However, the differences between histological subgroups and grades are subtle, and are susceptible to high inter-observer variability. Previously, additional data have suggested that the molecular profiles of gliomas are an improved predictor of survival compared with that of histology results (5). At present, most of studies have used information other than histological or clinical data to establish the molecular classifiers of glioma. The traditional molecular pathology of gliomas are summarized in Fig. 1. The key gene alternations in gliomas are summarized in Table II.

IDH mutation and chromosome 1p/19q codeletion. IDH1 and IDH2 are NADP⁺-dependent isocitrate dehydrogenases, catalyzing the oxidative decarboxylation of isocitrate to α -ketoglutarate (α -KG) and converting NADP to NADPH. Previous data implied that the mutations in the IDH1 and IDH2 genes were closely associated with the pathogenesis of malignant gliomas (18,37,38). Generally, patients with glioma with and without IDH mutations exhibit significantly different outcomes (12). In particular, IDH mutation, including R132H in the IDH1 gene, are commonly identified in WHO grade II and III disease (oligodendrogliomas, astrocytomas and secondary glioblastomas), suggesting that IDH mutations may be early events and promote the progression of gliomas (38). In addition, complete deletion of the short arm of chromosome 1 and the long arm of chromosome 19 (1p/19q co-deletion) is the molecular genetic signature of oligodendrogliomas, which occurs early in its pathogenesis (39). The 1p/19q co-deletion occurs in the majority of WHO grade II tumors, and has been a valuable diagnostic, prognostic and predictive biomarker for the management of oligodendroglial tumors (12).

TERT promoter mutations. TERT is a catalytic subunit of the telomerase and encodes a highly specialized reverse transcriptase. The role of TERT has been revealed by the frequent mutations of the TERT promoter (TERTp-mut) in gliomagenesis, but particularly in glioma (12,18). The mutations of the TERT promoter frequently occur in 2 loci, C228T and C250T, mapping -124 and -146bp, respectively, upstream of the TERT ATG site. The presence of TERTp-mut, creating binding sites for E26 transformation-specific/T-cell factor transcription factors, is significantly associated with higher mRNA expression. Increasing evidence has suggested that TERTp-mut also affects cancer susceptibility and results in poorer prognosis for patients with glioma (40).

MGMT promoter methylation. DNA methylation of the gene promoter may serve an important role in carcinogenesis. MGMT, as a coding DNA repair gene, is crucial for genome stability. During DNA replication and transcription, the MGMT gene may repair the naturally occurring mutagenic DNA lesion O-6-methylguanine back to guanine, preventing mismatch and errors. A number of studies have demonstrated that the methylation state of the MGMT gene is closely associated with the response to temozolomide (41). Specifically, if the promoter is methylated, the treatment is more effective; otherwise, the patient is not sensitive, suggesting that MGMT promoter methylation is a favorable predictor for overall survival and progression-free survival in glioma (42,43). At present, MGMT has also been revealed to be a useful tool for increasing gene therapy efficiency, and with applications in clinical detection (44).

Fusion genes. Gene rearrangements and the consequent fusion proteins serve an important role in tumorigenesis. It was previously demonstrated that a recurrent gene fusion event involving the protein tyrosine phosphatase receptor type Z1 (PTPRZ1) and MET proto-oncogene, receptor tyrosine kinase (MET) genes, termed the ZM fusion, was identified in 15% of secondary glioblastomas (45). In this fusion event, the PTPRZ1 promoter was activated to

additionally promote the expression of full-length MET, leading to MET overexpression. Patients with ZM fusion exhibited more aggressive phenotypes. The recurrent nature of the ZM fusion suggests that ZM fusion is associated with GBM migration and invasion, participates in PIK3CA signaling, and results in a poorer prognosis, supporting ZM as a potential GBM therapeutic target. In addition, the fibroblast growth factor receptor (FGFR)-transforming acidic coiled-coil containing protein (TACC) was the first well-characterized gene fusion event in GBMs (46-48). These fusion proteins include the tyrosine kinase domain of FGFR and the coiled-coil domain of TACC proteins. There are 2 subtypes of the FGFR-TACC gene fusion protein, FGFR3-TACC3 (F3-T3) and FGFR3-TACC1, in GBMs. Previously, Bao *et al* (45) indicated that F3-T3 was associated with oxidative phosphorylation and mitochondrial biogenesis. FGFR-TACC gene fusion may also provide a promising target for GBM treatment.

4. Conclusions

Within the previous decade, the volume of newly-published biological data has grown rapidly, and has increased understanding of the key genomic alternations in human glioma. At present, several glioma-associated genomic studies have been initiated, including TCGA and the CGGA, aiming to generate and comprehensively describe the multi-dimensional glioma genome. These projects provided unprecedented and publicly available glioma datasets, used widely by the scientific community. To provide improved understanding of the genetics of glioma, several studies have classified glioma into subtypes and revealed their associations with clinical parameters, assisting in the generation of novel cancer therapies, diagnostic methods and preventive strategies.

Although malignant glioma remains incurable, treatment options have been expanding and improving due to improved understanding of the complex molecular biology of these tumors. Based on the 2016 WHO organization classification of brain tumors, diffuse gliomas are defined by histopathology and molecular pathology, particularly for molecular diagnosis. At present, several key genes in glioma have been used as biomarkers for predicting outcome and guiding chemoradiotherapy, including MGMT promoter methylation. As important biological molecules, non-coding RNAs are emerging as biomarkers or potential targets for glioma treatment (49-52). Future studies will also generate additional biological glioma data that may reveal novel biological markers as therapeutic targets/candidates in the treatment of tumors.

Acknowledgements

The authors would like to acknowledge Dr Fanlin Meng at the School of Medicine, Tsinghua University, Beijing, China for her assistance in revising the manuscript.

Funding

The present study was supported by The National Key Research and Development Plan (grant no. 2016YFC0902500).

Availability of data and materials

Not applicable.

Authors' contributions

All authors participated in the design and final review of the manuscript. JC and ZZ conceived the review. ZZ and KZ drafted the manuscript. ZW and KW collected the information on data resources. XL and FW collected the information on molecular profiles. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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