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Original Article

Understanding the molecular profiling of diffuse gliomas classification: A brief overview

Edgar G. Ordóñez Rubiano[1,2,3], Matías Baldoncini[4], Alba Lucía Cómbita[5,6], César Payán-Gómez[7], Diego F. Gómez-Amarillo[8], Fernando Hakim[8], Luisa Fernanda Figueredo[9], Valeria Forlizzi[10], Carlos Castillo Rangel[11], Sabino Luzzi[12], Alvaro Campero[13], Rafael Parra-Medina[3,14]

[1]Department of Neurological Surgery, Fundación Universitaria de Ciencias de la Salud, Hospital de San José - Sociedad de Cirugía de Bogotá, [2]School of Medicine, Universidad Nacional de Colombia, [3]Research Institute, Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia, [4]Department of Neurosurgery, San Fernando Hospital, San Fernando, Argentina, [5]Departament of Microbiology, Universidad Nacional de Colombia, [6]Translational Research Group in Oncology, Instituto Nacional de Cancerología, Bogotá, [7]Academic direction, Universidad Nacional de Colombia - Sede de La Paz, La Paz, [8]Department of Neurosurgery, Hospital Universitario Fundación Santa Fé de Bogotá, Bogotá, Colombia, [9]Department of Psychiatry, New York University Langone Health, New York City, USA, [10]Department of Anatomy, University of Buenos Aires, Buenos Aires, Argentina, [11]Department of Neurosurgery, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico, [12]Department of Neurosurgery, University of Pavia, Polo Didattico "Cesare Brusotti", Pavia, Italy, [13]Hospital Padilla de Tucuman, Tucuman, Argentina, [14]Department of Pathology, Instituto Nacional de Cancerología Bogotá, Bogotá, Colombia.

E-mail: *Edgar G. Ordóñez-Rubiano - egordonez@fucsalud.edu.co; Matias Baldoncini - drbaldoncinimatias@gmail.com; Alba Lucía Cómbita - alcombitar@unal.edu.co; César Payán-Gómez - cepayang@unal.edu.co; Diego F. Gómez-Amarillo - diegogomezncx@gmail.com; Fernando Hakim - fhakimd@gmail.com; Luisa Fernanda Figueredo - lf.figueredo1341@gmail.com; Valeria Forlizzi - vforlizzi@gmail.com; Carlos Castillo Rangel - neuro_cast27@yahoo.com; Sabino Luzzi - sabino.luzzi@unipv.it; Alvaro Campero - alvarocampero@yahoo.com.ar; Rafael Parra-Medina - rafa.parram@gmail.com

***Corresponding author:**
Edgar G. Ordóñez-Rubiano, Department of Neurological Surgery, Fundación Universitaria de Ciencias de la Salud, Hospital de San José - Sociedad de Cirugía de Bogotá, Colombia.
egordonez@fucsalud.edu.co

Received : 04 March 2023
Accepted : 04 June 2023
Published : 30 June 2023

DOI
10.25259/SNI_209_2023

Quick Response Code:

ABSTRACT

Background: Gliomas represent almost 30% of all primary brain tumors and account for 80% of malignant primary ones. In the last two decades, significant progress has been made in understanding gliomas' molecular origin and development. These advancements have demonstrated a remarkable improvement in classification systems based on mutational markers, which contribute paramount information in addition to traditional histology-based classification.

Methods: We performed a narrative review of the literature including each molecular marker described for adult diffuse gliomas used in the World Health Organization (WHO) central nervous system 5.

Results: The 2021 WHO classification of diffuse gliomas encompasses many molecular aspects considered in the latest proposed hallmarks of cancer. The outcome of patients with diffuse gliomas relies on their molecular behavior and consequently, to determine clinical outcomes for these patients, molecular profiling should be mandatory. At least, the following molecular markers are necessary for the current most accurate classification of these tumors: (1) isocitrate dehydrogenase (IDH) *IDH-1* mutation, (2) 1p/19q codeletion, (3) cyclin-dependent kinase inhibitor 2A/B deletion, (4) telomerase reverse transcriptase promoter mutation, (5) α-thalassemia/mental retardation syndrome X-linked loss, (6) epidermal growth factor receptor amplification, and (7) tumor protein *P53* mutation. These molecular markers have allowed the differentiation of multiple variations of the same disease, including the differentiation of distinct molecular Grade 4 gliomas. This could imply different clinical outcomes and possibly impact targeted therapies in the years to come.

Conclusion: Physicians face different challenging scenarios according to the clinical features of patients with gliomas. In addition to the current advances in clinical decision-making, including radiological and surgical techniques, understanding the disease's molecular pathogenesis is paramount to improving the benefits of its clinical treatments. This review aims to describe straightforwardly the most remarkable aspects of the molecular pathogenesis of diffuse gliomas.

Keywords: Classification, Diffuse glioma, Glioblastoma, Glioma, Molecular pathology

INTRODUCTION

Gliomas represent about 30% of all primary brain tumors and are responsible for the majority of primary brain tumor deaths.[37,56] Diffuse gliomas are believed to originate from neuroglial stem cells and are classified histologically as astrocytomas, oligodendrogliomas, and glioblastomas (GBMs) based on morphologic similarities to neuroglial cell types found in normal tissue. They are classified according to the tumor's location (e.g., midbrain or thalamus), or also according to their characteristic patterns of differentiation, and features of anaplasia. The absence or presence of anaplastic attributes is used to assign grades of malignancy from Grade I to IV according to the 2007 World Health Organization (WHO) classification of the central nervous system (CNS) (WHO CNS3).[28-30] To date, diffuse gliomas are still classified by location and by their histology. Even though, this is not enough in terms of survival and chemo/radiosensitivity characterization. Several studies in the last decades have examined the molecular features of these tumors and have intended to correlate these findings with the clinical behavior and the prognosis of these patients. As a result, the last two consecutive 2016 (WHO CNS4)[29] and 2021 (WHO CNS5)[30] editions of the WHO classification have also included molecular profiling.

In different scenarios, health-care providers of different specialties are involved in the treatment of patients with gliomas and should be familiarized with terminology regarding patients' tumor diagnoses. Neurooncologists and neurologists as well as neurosurgeons should understand not only the terminology of molecular profiling but also the biological meaning and the implications behind these terms. In this review, we aim to describe and summarize the most remarkable aspects of the molecular pathogenesis of adult diffuse gliomas.

MATERIALS AND METHODS

The authors performed a narrative review of the literature including each molecular marker described for adult diffuse gliomas used in the WHO CNS5. A MEDLINE/PUBMED search was based on the references of retrieved literature. This review included a comprehensive overview of the 3rd, 4th, and 5th editions of the WHO classification.

RESULTS

Histopathological classification

According to the WHO CNS3, gliomas include astrocytomas of various grades (diffuse astrocytoma [Grades II and III] and GBM [Grade IV]), oligodendrogliomas (Grades II and III), and mixed oligoastrocytomas (Grades II and III) [Table 1].[56] Despite worldwide use of this classification given the relatively easy way to determine cell predominance at the microscopic view, multiple concerns remained in terms of mixed cellular cases and lack of additional information to investigate for clinical prognosis. In the last decade, there has been meaningful progress in the comprehension of the molecular pathogenesis of gliomas. These advancements have improved diagnostic and classification systems.[28-30] Furthermore, a better understanding of the molecular pathogenesis of these tumors has identified new molecular targets and has outlined therapeutic strategies that could improve the results in the treatment of this pathology. However, at present, the classic prognostic factors, such as the patient's age, general functional status, and neurological status, as well as the extent of resection, continue to determine the prognosis of these patients.[56] This highlights the importance of identifying other molecular markers that allow defining the prognosis of this pathology from diagnosis and identifying potential therapeutic targets that allow establishing new and more efficient therapeutic strategies.

Molecular classification

The WHO Grade II–III gliomas are the most prevalent gliomas in young adults and are characterized by diffuse infiltration of the brain and their proclivity for recurring and malignant progression. Histological classification had previously distinguished astrocytic, oligodendroglial, and mixed oligoastrocytic tumors. However, molecular markers have now revealed evidence of only two subtypes: (1) the astrocytic genotype, which is characterized by mutations in tumor protein P53 (*TP53*), often accompanied by a mutation in the α-thalassemia/mental retardation syndrome X-linked (*ATRX*) gene, and (2) the oligodendroglial genotype, which is characterized by the codeletion of 1p and 19q chromosomal arms (1p/19q codeletion), associated with the mutation of the telomerase reverse transcriptase (*TERT*) promoter (*TERTp*).[21,47] Even though, the oligoastrocytic genotype was still included in the next version of the WHO classification, published in 2016,[29] where its differentiation remained highly controversial [Table 2]. The WHO CNS4 still gave substantial importance to histological information, and this certainly influenced the presence of the oligoastrocytoma in this version.

To improve the classification of diffuse gliomas, the WHO CNS5[30] eliminated oligoastrocytoma as a separate entity and converged in astrocytomas or oligodendrogliomas. This version summarized the most important features of molecular profiling of diffuse glioma, leading to better characterization. This edition included the loss of *ATRX*, mutation of the *TP53*, the cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) gene deletion, the epidermal growth factor receptor (*EGFR*) amplification, and *TERTp* mutation [Table 3 and Figure 1]. In addition, the nomenclature was

Table 1: 2007 WHO classification of gliomas based on histopathology.

Phenotype	Subtype	Histological findings	Grade
Astrocytic	Pilocytic astrocytoma	Low cell proliferation	I
	Diffuse astrocytoma	Marked hypercellularity	II
	Anaplastic astrocytoma	Elevated mitotic activity, cellular atypia	III
	Glioblastoma	Necrosis and microvascular proliferation	IV
Oligodendroglial	Oligodendroglioma	Marked hypercellularity	II
	Anaplastic oligodendroglioma	Elevated mitotic activity, cellular atypia	III
Oligoastrocytic	Oligoastrocytoma	Marked hypercellularity	II
	Oligoastrocytoma	Elevated mitotic activity, cellular atypia	III

WHO: World Health Organization

Table 2: 2016 WHO classification of diffuse gliomas.

IDH status	1p/19q Codeletion	Subtype	Grade
IDH-wildtype	Absent	Diffuse astrocytoma, IDH-wildtype	II
			III
	Absent	Glioblastoma, IDH-wildtype	IV
IDH-mutant	Present	Oligodendroglioma	II
			III
	Present	Diffuse astrocytoma, IDH-mutant	II
			III
	Present	Glioblastoma, IDH-mutant Oligoastrocytoma	IV

WHO: World Health Organization, IDH: Isocitrate dehydrogenase

Table 3: 2021 WHO classification of diffuse gliomas.

IDH status	Molecular profile	Subtype	Grade
IDH-wildtype	Nonspecified	Diffuse astrocytoma, *IDH*-wildtype	2
			3
	Chromosome 7 gain, Chromosome 10 loss, *EGFR* amplification, *TERT* promoter mutation	Glioblastoma, *IDH*-wildtype	4
IDH-*mutant*	1p/19q Codeletion	Oligodendroglioma	2
			3
	ATRX loss, *TP53* mutation	Diffuse astrocytoma, *IDH*-mutant	2
			3
	ATRX loss, *TP53* mutation, *CDKN2A/B* deletion	Astrocytoma, *IDH*-mutant	4

WHO: World Health Organization, IDH: Isocitrate dehydrogenase, EGFR: Epidermal growth factor receptor, TERT: Telomerase reverse transcriptase, ATRX: α-thalassemia/mental retardation syndrome X-linked, TP53: Tumor protein P53, CDKN2A/B: Cyclin-dependent kinase inhibitor 2A/B

changed from Roman numbers to Arabic numbers to refer to the histological grade. This classification has made it possible to differentiate new entities, differentiating mutant isocitrate dehydrogenase (IDH) Grade 4 astrocytoma from GBM, which necessarily have the *IDH* wildtype status. This has made it possible to partially clarify why some Grade 4 gliomas have a better prognosis than others and reclassify the previously called "secondary GBM." Undoubtedly, in the near future, the complementary study with transcriptomics and proteomics will improve this classification, showing the variety of pathologies framed within the group of diffuse gliomas. Thus, in addition to the histopathological study, the complete molecular profile for the study of diffuse gliomas should include preferably the analysis of the presence or absence of (1) *IDH-1* mutation, (2) 1p/19q codeletion, (3) loss of *ATRX*, (4) *TP53* mutation, (5) *CDKN2A/B* deletion, (6) *EGFR* amplification, (7) *TERTp* mutation, as well as (8) gain of chromosome 7, and (9) loss of chromosome 10 [Table 4]. Most of these genes encode receptor tyrosine kinases and their downstream signaling companions. Here, we will resume these mutational markers and their role in diffuse glioma pathogenesis.

Hallmarks of cancer: Diffuse gliomas

As the global tendency is to characterize and classify tumors by their molecular behavior, it is of major importance to enhance the intrinsic properties of tumors described in the last decade. All gliomas, but more specifically GBM are recognized by their malignant behavior and their complex molecular biology. To understand these malignant properties, it is fundamental to comprehend the basis of cancer. Hanahan and Weinberg proposed the "*Hallmarks of Cancer*" as a set of functional capabilities that make cells their way from normalcy to neoplastic growth states, which are characteristics that are basic for their ability

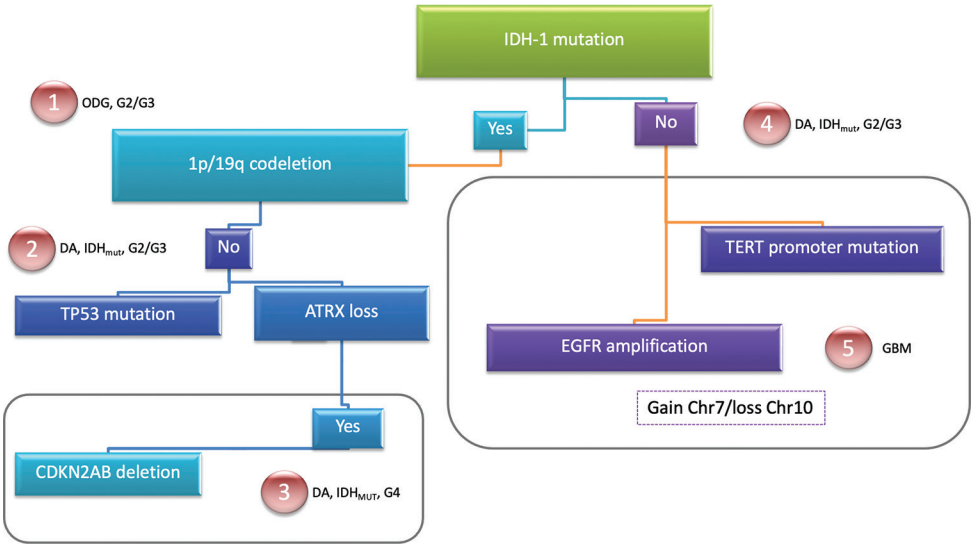

Figure 1: The World Health Organization Central Nervous System 5. Molecular biomarkers used for classifying diffuse gliomas. A simple resume for easy differentiation of the presence of mutations in each entity is demonstrated. Sequential acquisition of markers can be performed to perform a correct diagnosis. The five different subtypes of diffuse gliomas are shown. DA: Diffuse astrocytoma, ODG: Oligodendroglioma, GBM: Glioblastoma, IDH_{mut}: Isocitrate dehydrogenase mutated, ATRX: Alfa-thalassemia/mental retardation syndrome X-linked, CDKN2AB: Cyclin-dependent kinase inhibitor 2A/B, EGFR: Epidermal growth factor receptor, TERT: Telomerase reverse transcriptase.

to form cancer.[17] Six hallmarks were initially proposed, including (1) the acquired capabilities for sustaining proliferative signaling, (2) evading growth suppressors, (3) resisting cell death, (4) enabling replicative immortality, (5) inducing/accessing vasculature, and (6) activating invasion and metastasis. Afterward, in 2011, two additional enabling characteristics were added: (1) genome instability and mutation and (2) tumor-promoting inflammation. Furthermore, two additional "emerging hallmarks" were included: (1) deregulating cellular energetics and (2) avoiding immune destruction.[18] In the updated 2022 version of the proposed hallmarks of cancer, a total of 14 hallmarks were included in the study [Figure 2].[16] In the 2022 version, the 2011 "emerging hallmarks" and the enabling characteristics were included in the core hallmarks. In addition to these 10, the following emerging hallmarks were also incorporated: (1) unlocking phenotypic plasticity and (2) nonmutational epigenetic reprogramming, and two enabling characteristics were included as well: (1) polymorphic microbiomes, and (2) senescent cells. Recently, Belotti *et al.* described prognostic neurotransmitter receptor genes that may be associated with cancer hallmarks in gliomas. These genes were differently associated when comparing low-grade gliomas (LGG) and GBM, particularly with immune response.[6] Despite several studies that have explored these hallmarks separately, further studies are needed to explore these hallmarks as wholesome in gliomas.

Core mutational markers

Core mutational markers have been described for diffuse gliomas given the importance of differentiating separate entities in terms of biological behavior and the influence on clinical prognosis. These markers have been identified in multiple studies demonstrating the presence or not in each different glioma subtype. Hereafter, we resume the most valuable information regarding these core molecular markers.

IDH-1 mutation

Diffuse gliomas of both genotypes can carry mutations in the gene for the enzyme IDH 1 (*IDH1*) [Figure 3] or, less frequently, in *IDH2*.[4,59] *IDH1* and *IDH2* are very similar genes and will be used collectively as *IDH* hereafter. The *IDH* mutation likely represents the tumor-initiating alteration in most diffuse gliomas, except for the rare tumors arising in patients with a germline *TP53* mutation who secondarily acquire *IDH* mutations.

IDH enzymes normally catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (alpha-ketoglutarate [α-KG]), thus generating nicotinamide adenine dinucleotide phosphate (NADPH) from NADP+. When the gene is mutated, the enzyme shows a gain in function to produce D-2-hydroxyglutarate (D-2HG) from α-KG, demonstrating a decreased NADPH production, which probably predisposes cells to oxidative stress.[44] Elevated levels of D-2HG in IDH_{mut}

Table 4: Molecular profile of diffuse gliomas.

Marker	Molecular implications	Clinical implications	Tests used for diagnosis*
IDH 1/2 mutation	Profound effects on differentiation patterns, and metabolic profiles.	If the mutation is present has prolonged survival.	PCR, immunochemistry
1p/19q codeletion	A process that allows functioning apoptotic pathways to persist or to the loss of gene products that drive treatment resistance or confer tumor suppression.	If the mutation is present, patients have a prolonged survival as well as increased chemo/radiosensitivity.	FISH, LOH-PCR, MLPA
Loss of *ATRX*	The loss of ATRX in gliomas promotes ALT and has been strongly associated with DNA damage and replicative stress.	If the mutation is present, patients demonstrate a worse prognosis compared to 1p/19q codeleted IDH_{mut} gliomas. In noncodeleted IDH_{mut} gliomas when present correlates to a better prognosis.	PCR, immunochemistry
TP53 mutation	Evasion of apoptosis, migration, proliferation, as well as invasion	Increased progression rate and lower OS.	NGS, immunochemistry
CDKN2A/B deletion	Increased Rb phosphorylation, the release of elongation factor, and uncontrolled activation of the genes involved in the progression from G1 to the S phase.	Poor prognosis and limited OS in IDH_{mut} astrocytoma.	FISH
EGFR amplification (2–7 exons)	Promotes cell proliferation and increased cell survival by blocking apoptosis.	Promotes invasion, proliferation, and resistance to radiotherapy and chemotherapy	NGS, PCR
TERT promoter mutation	The abnormal reactivation of the telomerase complex generates lengthened telomeres.	In triple-positive LGG the *TERTp* mutation represents a better prognosis, while when it's present isolated in IDH-wildtype tumors, patients have the worse overall prognosis.	Sanger
Gain of chromosome 7 and loss of chromosome 10		Lower survival rates, including the presence of the gain of chromosome 7 alone, the loss of chromosome 10 or concomitancy of both alterations.	FISH

*Based on recommendations of the American College of Pathologists. ATRX: α-thalassemia/mental retardation syndrome X-linked gene, CDKN2A/B: Cyclin-dependent kinase inhibitor 2A gene, EGFR: Epidermal growth factor receptor, IDH: Isocitrate dehydrogenase, FISH: Fluorescence *in situ* hybridization, LOH-PCR: Loss of heterozygosity polymerase chain reaction, MLPA: Multiplex-ligation probe amplification analysis, NGS: Next generation sequencing, ALT: Alternative lengthening of telomeres, OS: Overall survival, DNA: Deoxyribonucleic acid, TERT: Telomerase reverse transcriptase, LGG: Low-grade glioma.

cells have been shown to competitively inhibit the activity of α-KG-dependent dioxygenases, including demethylated histones and the 5-methylcytosine hydroxylases of the "ten-eleven translocation" (TET) enzymes. D-2HG is an oncometabolite that has been associated with profound effects on cellular epigenetic programs, differentiation patterns, and metabolic profiles.[40] This inhibition conducts to increased histone methylation and hypermethylation of multiple CpG islands in deoxyribonucleic acid (DNA), which is a characteristic epigenetic marker of IDH_{mut} gliomas that has been termed as the glioma CpG island methylator phenotype.[52] However, the *IDH* mutation alone is not enough to cause the development of glioma.[48] IDH_{mut} neuroglial progenitor or stem cells likely need to acquire additional genetic alterations to transform into astrocytomas (*ATRX* and *TP53* mutations) or oligodendrogliomas (1p/19q codeletion and *TERTp* mutations).

1p/19q codeletion

Reifenberger *et al.* were the first in demonstrating that oligodendroglial tumors show allelic deletions on 19q (deletions in different regions of the short arm of chromosome 19 with similar phenotype) and the majority of tumors with 19q loss also show loss of alleles on lp.[42] Afterward, it was demonstrated that combined 1p/19q loss was associated with chemosensitivity and prolonged survival in anaplastic oligodendrogliomas.[10] 1p/19q loss is mediated by an unbalanced translocation with whole-arm deletions as a consequence of the loss of the derivative chromosome (1;19) (p10;q10), while the reciprocal derivative (1;19) (q10; p10) chromosome is retained [Figure 4].[14,20] This is primordial because it explains why the combined loss of 1p and 19q is of increased significance than the loss of each chromosome arm individually.[39] The main reasons

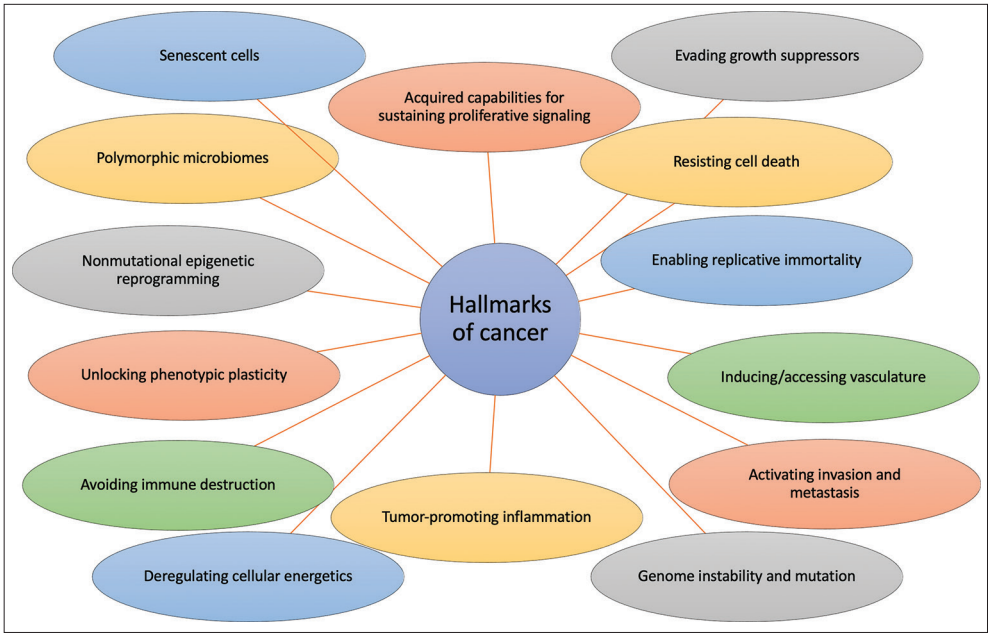

Figure 2: Core mutational hallmarks of cancer.

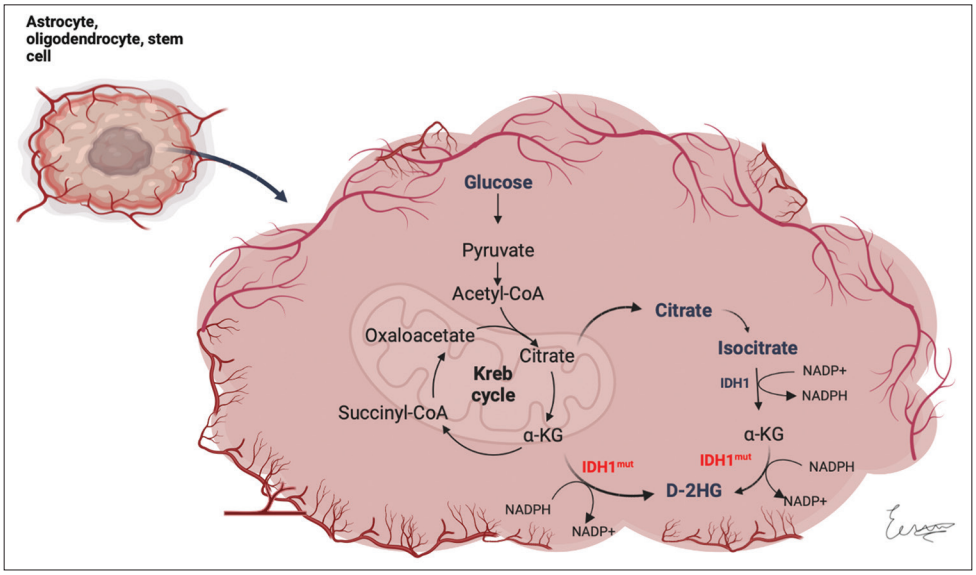

Figure 3: Impairment of cellular metabolism in IDH mutant diffuse gliomas. The enzyme isocitrate dehydrogenase 1 normally catalyzes the oxidative decarboxylation of isocitrate to form 2-oxoglutarate (α-KG). When the enzyme is mutated, it shows a gain in function to produce D-2-hydroxyglutarate from α-KG. α-KG: Alpha-ketoglutarate, IDH1: Isocitrate dehydrogenase 1, IDH1mut: Mutated isocitrate dehydrogenase 1, D-2HG: D-2 hydroxyglutarate. (Created with www.biorender.com), NADPH: Reduced nicotinamide adenine dinucleotide phosphate, NADP+: Oxidized nicotinamide adenine dinucleotide phosphate.

why 1p/19q codeletion is correlated with better outcomes remain unclear, but it is probably associated with a process that allows functioning apoptotic pathways to persevere or the loss of gene products that handle treatment resistance or grant tumor suppression.[39]

Loss of ATRX

The role of the *ATRX* gene in cancer has emerged in the past decade. The status of the ATRX is now pivotal for glioma classification and has been included as part of the

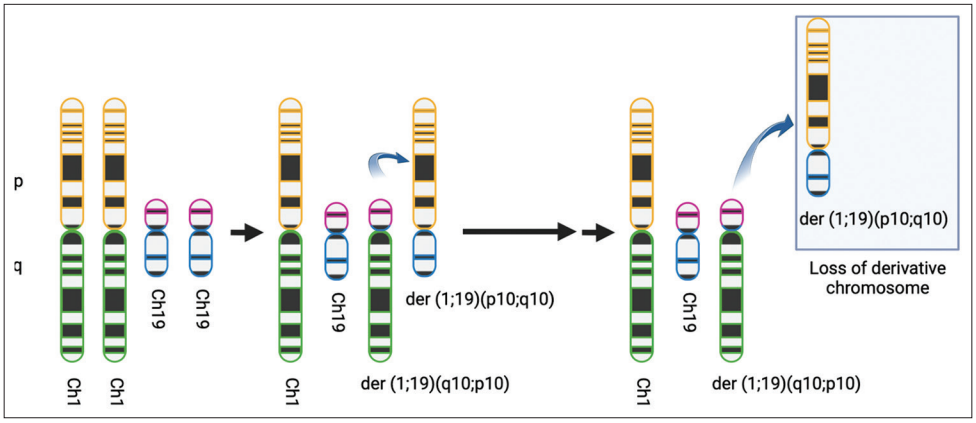

Figure 4: Codeletion of 1p/19q. It is believed that an unbalanced whole-arm translocation between chromosomes 1 and 19 creates two derivatives chromosomes: der (1;19) (q10;p10) and der (1;19) (p10;q10). This translocation generates the loss of derivative chromosome der (1;19) (p10;q10), which contains 1p and 19q. (Created with www.biorender.com).

molecular profile for glioma characterization.[30] The ATRX protein is part of the chromatin remodeling proteins and helps to maintain genomic stability through its deposition of the replication-independent histone variant H3.3 at telomeres.[38] Mutations on *ATRX* have been associated with the Alternative Lengthening of Telomeres (ALT) mechanism.[23] The loss of *ATRX* in gliomas promotes ALT and has been strongly associated with DNA damage and replicative stress.[9] Mechanisms of *ATRX* loss include deletions, mutations, or gene fusions, which may impact ALT and correlate with *TP53* mutation.[36] The concurrence of *IDH1*, *TP53*, and *ATRX* mutations are characteristic of the IDH_{mut} astrocytomas,[30] otherwise, the concurrence of 1p/19q codeletion and *ATRX* loss is extremely rare. *ATRX* mutations have been shown to correlate with worse progression-free survival and overall survival (OS) in IDH_{mut} astrocytomas in comparison with oligodendrogliomas. However, *ATRX* mutations demonstrated better progression-free survival and OS when looking only within the group of IDH_{mut} astrocytomas.[24,57]

TP53 mutation

TP53 is a tumor suppressor. Normal TP53 protein functions as an inhibitor of cellular replication when sustained DNA damage and its gene mutation leads to an impaired protein that alters its ability to bind DNA and prevent cell replication.[41] In gliomas, the mutation in *TP53* is one of the most commonly detected alterations and acts as a remarkable molecular biomarker for therapeutic approaches.[15] In GBM, TP53 pathway dysregulation has been related to different cellular processes including evasion of apoptosis, migration, and proliferation, as well as invasion, among different processes.[54,58] The Cancer Genome Atlas (TCGA) (https://www.cancer.gov/tcga) demonstrated that *TP53* mutation was present in 49% of all patients with LGG,[15] while it was shown to be the most frequently mutated gene in GBM.[11] Gliomas with a single mutation that codes for the R273C amino acid change have been found to have an increased progression rate and lower OS.[32]

CDKN2A/B homozygous deletion

According to the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy — Not Official WHO (cIMPACT-NOW) recommendation,[27] the WHO CNS5 adopted the *CDKN2A/B* homozygous deletion into the molecular characterization of diffuse gliomas. The prior consideration of malignant progression to secondary GBM was primarily confined to tumors with an astrocytic genotype. This malignant progression involves the homozygous deletion of the *CDKN2A/B* locus. As mentioned before this entity is now classified as "Astrocytoma, IDH mutant, Grade 4."[30] The impact of this mutation relies on the poor prognosis and limited OS in IDH_{mut} astrocytoma, regardless of histological tumor grade (OS ~3y).[2,43,51]

CDKs are core regulatory molecules that determine cellular progression through the cell cycle. Extracellular signals lead to complex formation between D-type cyclins and cyclin-dependent kinases 4 and 6 (CDK4/CDK6) [Figure 5]. The generation of this complex promotes retinoblastoma protein (pRB) phosphorylation, as well as the release of elongation factor, and activation of genes related to the transition from the G1 to S phase.[43] *CDKN2A* is a gene located at chromosome 9 (band p21.3) and codes for the tumor suppressor proteins $p16^{INK4a}$ (aka INK4a) and p14 (aka alternate reading frame), which regulate the activities of p53 and the pRB in tumor suppression. p14 triggers cell-cycle arrest or apoptosis by inactivating the mouse double minute

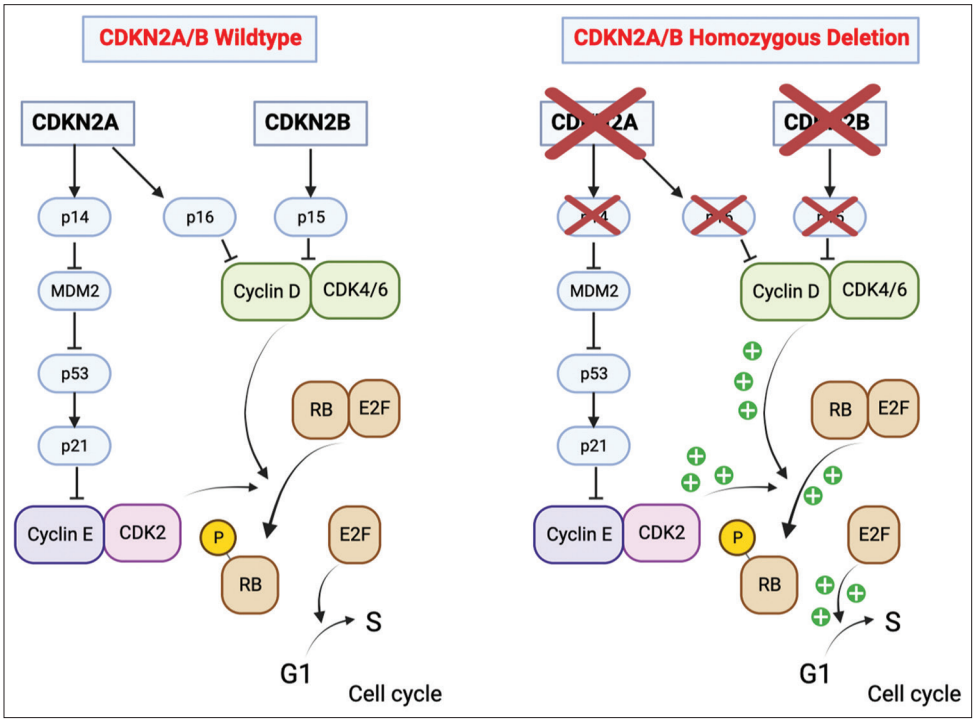

Figure 5: Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) homozygous deletion. In nonmutated cells, the CDKN2A gene synthesizes p16 and p14. p16 binds to and inactivates CDK4/6. The CDKN2B gene is adjacent to CDKN2A and encodes p15, which inactivates CDK4/6. The p14 protein is an alternate reading frame protein and prevents p53 degradation by inhibiting MDM2 activity. This generates the activation of p21, which binds to and inhibits the activity of CDK2. By binding to these cyclin-dependent kinases, p14, p15, and p16 block cell cycle progression from G1 to the S phase. On the other hand, when CDKN2A/B is homozygously deleted, the cells are unable to synthesize these tumor suppressor proteins. Consequently, there is an unrestricted generation of complexes between cyclins and cyclin-dependent kinases, which leads to increased Rb phosphorylation, a release of elongation factor, and uncontrolled activation of the genes involved in the progression from G1 to the S phase. (Created with www.biorender.com), CDK4/6: Cyclin-dependent kinases 4 and 6, MDM2: Mouse double minute 2 homologous, RB: retinoblastoma protein, CDK2: Cyclin-dependent kinase 2.

2, which is an E3 ubiquitin-protein ligase targeting p53 for destabilization. This process generates p21 activation, which inhibits the activity of the cyclin/CDK complex, especially CDK2. In addition, $p16^{INK4a}$ promotes pRB-mediated cell-cycle checkpoints by inhibiting CDK4 that phosphorylates and inactivates pRB.[31] On the other hand, the *CDKN2B* gene, which is adjacent to *CDKN2A*, encodes the p15 protein (aka INK4B). This protein binds to CDK4/CDK6 and inactivates them, controlling cell proliferation.[19] The inclusion of the *CDKN2A/B* deletion into the WHO CNS5 elevates its status to that considered to microvascular proliferation and necrosis.

EGFR amplification

EGFR is a cell transmembrane tyrosine kinase receptor, and its gene (*EGFR*) is in the chromosome band 7p12.1.[46] *EGFR* can be modified in several ways in diffuse gliomas especially in GBM by overexpression, amplification, and deletion mutants, among others.[46] Amplifications are a type of mutation that results in various copies of genes in chromosomal regions that induce the overexpression of proteins in neoplastic cells.[26] *EGFR* is one of the most amplified genes in cancer.[1] Particularly, in GBM, the *EGFR* gene amplification is associated with EGFR overexpression,[8] that leads to the activation of intracellular signaling pathways that promote cell proliferation and increased cell survival by blocking apoptosis. Some of the most remarkable activated pathways include RAS/RAF/MEK/MAPK and PI3K/Akt.[33] Amplified DNA can be presented in different forms, including as extrachromosomal elements called double minute chromosomes, which is the most frequent *EGFR* amplification pattern in GBM.[26] Some studies have suggested that *EGFR* amplification promotes invasion, proliferation, and resistance to radio/chemotherapy.[12,35,46] In terms of survival, literature is controversial. EGFR gene amplifications seem to change according to co-occurrence

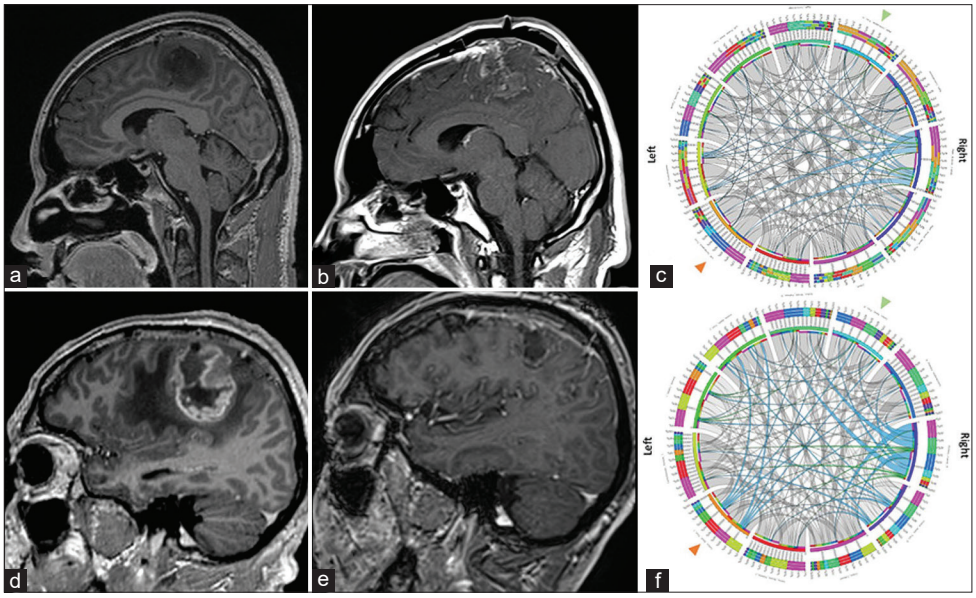

Figure 6: Neuroimaging of an oligodendroglioma Grade 2 and of an isocitrate dehydrogenase (IDH) IDH_{mut} astrocytoma, Grade 4. Case 1. Oligodendroglioma Grade 2. (a) Preoperative axial T1 postcontrast imaging demonstrating a nonenhancing perirolandic hypointense tumor. (b) Immediate postoperative enhanced magnetic resonance imaging (MRI) demonstrating near total resection of the tumor. (c) Preoperative connectivity map. White fibers are arranged in a symmetric distribution in both, left and right cortical tracts, noting in blue an increased signal diffusion in the right Aslant tract. Green arrowhead: Right corticospinal tract, Orange Arrowhead: Left corticospinal tract. Case 2. IDHmut astrocytoma, grade 4. (d) Preoperative enhanced MRI demonstrates a large enhancing perirolandic tumor consistent with a high-grade glioma. (e) 3-month follow-up MRI demonstrates adequate control with no enhancing tumor. (f) Preoperative connectivity map. White fibers are arranged in a symmetric distribution in both, the left and right cortical tracts, note in blue an increased signal diffusion in the right Aslant tract, the left corticospinal tract, and the right external capsule. Green arrowhead: Right corticospinal tract, Orange Arrowhead: Left corticospinal tract.

with other mutations including *EGFRvIII* deletion[50] or homozygous *CDKN2A* deletion.[7]

TERT promoter mutation

Telomerase is a protein mainly conformed by human telomerase ribonucleic acid and TERT. The telomerase is located within the cell nucleus, and its function is to synthesize a repetitive nucleotide sequence (TTAGGG) while creating the telomeres at the end of chromosomes to protect genomic DNA.[34] TERT is the catalytic subunit of the human telomerase, which is responsible for catalyzing the addition of the nucleotides in the TTAGGG sequence.[49] *TERTp* mutation derives in increased telomerase activity and lengthen telomeres.[13] Reactivation of TERT occurs due to mutations in hotspots located at −124 bp and −146 bp upstream of the *TERT* translation start site. There is an activation of somatic point mutations that substitute a cytosine for a thymidine (C > T) at position 228 (C228T) and/or 250 (C250T) of the *TERTp*. These mutually exclusive mutations are typically heterozygous and create 11 base pair sequences ("CCCGGAAGGGG"), a *de novo* E26 transformation-specific family transcription factor binding motif.[5]

Killela *et al*. reported that *TERTp* mutations were present in about 80% of GBM and oligodendrogliomas.[22] This suggests that *TERTp* mutation could even be more important in the cascade of mutation for gliomagenesis in comparison to other molecular markers. *TERTp* mutations represent a major mechanism of telomerase upregulation in gliomas and are critical for characterizing and classifying GBM. This poses a paramount role of telomerase and telomere elongation in the pathogenesis of gliomas.[3] Significance of *TERTp* mutation differs depending on the IDH status and the presence or not of 1p19q codeletion. When there is a triple-positive LGG (positive for *TERTp* mutation, *IDH* mutation, and 1p19q codeletion), the *TERTp* mutation represents a better prognosis, while when its present isolated in IDH-wildtype tumors, patients have the worse overall prognosis, even worse than triple-negative gliomas.[13]

Gain of chromosome 7 and loss of chromosome 10

Gain of chromosome 7 alone has shown an increased recurrence of gliomas in the pediatric population.[45] Particularly when sequencing GBM, a common pattern of concurrence of gain of chromosome 7 and loss of chromosome

10 has been described as a hallmark in this entity. In fact, this alteration has been identified in 100% of the classical subtype of GBM.[53] Lopez-Gines *et al*. found that lower survival rates in GBM were associated with the monosomy of chromosome 10, trisomy of chromosome 7, and the concurrence of both alterations.[25] Chromosome 7 gain and loss of chromosome 10, as well as *EGFR* amplification and *TERTp* amplification, are now used as hallmarks for GBM classification, distinguishing GBM from other diffuse glioma subtypes.[30] If needed, complementary analysis of chromosomal abnormalities should be added and addressed in GBM cases, particularly for chromosomes 7 and 10.

DISCUSSION

Glioma precision medicine

Just before the publication of the WHO CNS5, Weller *et al*. published the EANO guidelines of adulthood diffuse gliomas.[55] Despite these guidelines were based on the WHO CNS4, the in terms of integrated histomolecular classification the following recommendations remain the most updated for diffuse glioma: [55] (1) glioma classification should follow the most recent WHO CNS, complemented by cIMPACT-NOW updates, (2) IDH immunohistochemistry (R132H protein) and nuclear expression of ATRX should be performed routinely, (3) if IDH1 is negative then IDH 1 (codon 132) and IDH2 (codon 172) should be performed, (4) 1p/19q codeletion status should be determined in all IDH-mutant gliomas, (5) Methyltransferase promoter methylation status should be determined in GBM to guide in decision-making for the use of temozolomide, (6) *CDKN2A/B* homozygous deletions should be performed in IDH_{mut} astrocytomas (this should be prioritized after WHO CNS 5), and (7) Chromosome +7/−10 signature, EGFR amplification, and TERTp mutation should be tested in IDH_{wt} gliomas lacking microvascular proliferation and necrosis as histological features of the WHO Grade 4 to allow for a diagnosis of GBM.

In addition to separate all entities, the WHO CNS 5 allows to evaluate prognosis in terms of OS and chemo and radiosensitivity.[30] In the near future, many aspects including radiological assessment should be performed to differentiate these subtypes. Different approaches including radiological follow-up as well as evaluation of the connectome will guide adjuvant treatment and, if necessary, reoperations when indicated. Figure 6 demonstrates the radiological evaluation of an oligodendroglioma Grade 2 (1p/19q codeleted) in comparison with an IDH_{mut} astrocytoma, Grade 4. Advanced neuroimaging, in relation to molecular classification, would elucidate how the tumor impact on neural organization and will help to understand the biology of the different glioma subtypes.

CONCLUSION

Here, we resume some of the most important current markers used for the molecular classification of diffuse gliomas. The understanding of the genetic origin of the molecular features of gliomas is mandatory for neurosurgeons and neuro-oncologists. The literature regarding this topic is overwhelming and increases day by day. The complex molecular structure among the various type of gliomas generates the investigation of targets for treatment one of the most challenging tasks for neuroscientists in this era. The most remarkable molecular markers must be included in the study for the diagnosis of these tumors whenever possible to guide in a case-by-case manner the adjuvant treatment. Certainly, differentiating all genetic/molecular subtypes of diffuse gliomas will demonstrate why the prognosis changes are sometimes notable between one case and another, even for tumors in the same molecular group with the same extent of resection rates. Finally, complementary genomic and transcriptomic studies must continue to be performed, as they will help to elucidate the covered origins of molecular cascades and will guide us to a better understanding of these neoplasms.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Ordóñez-Rubiano EG, Baldoncini M, Cómbita AL, Payán-Gómez C, Gómez-Amarillo DF, Hakim F, *et al*. Understanding the molecular profiling of diffuse gliomas classification: A brief overview. Surg Neurol Int 2023;14:225.