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Review

Glioma epigenetics: From subclassification to novel treatment options

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ABSTRACT

Gliomas are the most common malignant primary brain tumors, of which glioblastoma is the most malignant form (WHO grade IV), and notorious for treatment resistance. Over the last decade mutations in epigenetic regulator genes have been identified as key drivers of subtypes of gliomas with distinct clinical features. Most characteristic are mutations in *IDH1* or *IDH2* in lower grade gliomas, and *histone 3* mutations in pediatric high grade gliomas that are also associated with characteristic DNA methylation patterns. Furthermore, in adult glioblastoma patients epigenetic silencing of the DNA repair gene *MGMT* by promoter methylation is predictive for benefit from alkylating agent therapy. These epigenetic alterations are used as biomarkers and play a central role for classification of gliomas (WHO 2016) and treatment decisions. Here we review the pivotal role of epigenetic alterations in the etiology and biology of gliomas. We summarize the complex interactions between "driver" mutations, DNA methylation, histone post-translational modifications, and overall chromatin organization, and how they inform current efforts of testing epigenetic compounds and combinations in preclinical and clinical studies.

1. Introduction

Gliomas are among the most common primary brain tumors in adults and account for over 70% of malignant brain tumors, of which glioblastoma is the most common and most malignant (World Health Organization [WHO] grade IV) with an incidence rate of 3.2 per 100 000 population [1]. The median survival is less than 2 years with the current standard of care of maximal safe resection, followed by combined radio-chemotherapy with the alkylating agent Temozolomide [2] that may be modestly improved with the addition of Tumor Treating Fields [3]. Glioblastomas are notorious for resistance to therapy, and despite numerous efforts, the addition of targeted agents against genetic or biological hallmarks of gliomas have largely failed [4]. Lower grade gliomas (LGG) WHO grade II and III are less common and affect younger patients. They have a better prognosis and show some sensitivity to therapy that both depend on the molecular subtype [5,6]. After resection LGG patients may first just be followed according to a "wait and see" strategy that depends on clinical and molecular risk factors, before entering treatment with different schemes of radio- or chemotherapy, or a combination thereof [6–8]. The optimal therapy is debated, however treatment related effects on cognitive function require risk-adapted (molecularly driven) treatment strategies, given that LGG patients may live more than 15 years [9].

2. Epigenetics of glioma

2.1. Epigenetic subtypes of gliomas

Insights into the molecular landscape of diffuse gliomas have revealed characteristic genetic and epigenetic profiles which have clarified their etiologic evolution [5,10–16] and allowed their classification into distinct molecular subtypes that have been integrated into the 2016 WHO classification (Fig. 1) [17]. Mutations in the epigenetic modulator genes isocitrate dehydrogenase 1 or 2 (*IDH1* or *IDH2*), and in the histone genes *H3F3A* or *HIST1H3 B* have become key biomarkers for tumor classification and emphasize the important role of epigenetic alterations as drivers in the evolution and biology of gliomas [10,12,18–20].

A point mutation in *IDH1* or *IDH2* (IDHmt) is characteristic for lower grade gliomas (WHO grade II/III), which are most prevalent in young adults. IDHmt gliomas are further subdivided into two major subtypes: oligodendrogliomas, with codeletion of chromosomal arms 1p/19q (1p/19q codel) that are usually associated with an activating mutation in the promoter of *TERT,* and astrocytomas, without 1p/19q codel. The latter are almost always associated with a mutation in *TP53,* and a mutation in *ATRX* that leads to loss of its nuclear expression, and diagnostically can be determined by immunohistochemistry [20]. Low grade gliomas without *IDH* mutation are termed IDH wild-type (IDHwt)

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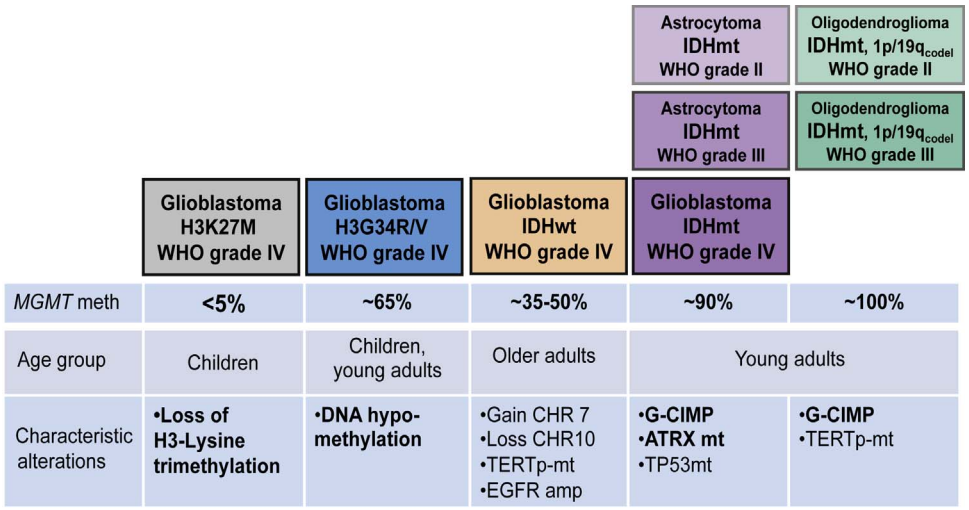

Fig. 1. Major genetic and epigenetic subgroups of gliomas. Characteristic epigenetic alterations are written in bold. CHR, chromosome; H3, histone 3; G-CIMP, glioma CpG island methylator phenotype.

astrocytomas and are considered a provisional entity by the 2016 WHO classification. Upon further genetic analyses they may be classified into other entities [21]. In glioblastomas IDHmt are infrequent (< 10%) [10], and are usually observed in younger patients whose tumors may have progressed from an IDHmt non-codeleted lower grade glioma WHO grade II or III [22]. The histone mutation H3K27 M is characteristic for pediatric midline high grade glioma and the H3G34R/V mutation for hemispheric high grade glioma in children and young adults [23]. Most interestingly, these epigenetic driver mutations are associated with characteristic DNA methylation profiles, display characteristic age distributions and tumor locations that is suggestive of brain development related associations and are considered different diseases Fig. 1 [12,23].

2.2. DNA methylation

The most commonly studied epigenetic alterations in cancer comprise changes in DNA methylation, in particular methylation at the 5th position of cytosines at CpG sites, resulting in 5-methylcytosine, also known as the “fifth base” of DNA. There are several DNA methyltransferases involved in DNA methylation, of which all use S-adenosyl-L-methionine as source of methyl groups. DNMT1 preferentially methylates hemi-methylated DNA and is responsible for maintenance of DNA methylation patterns during replication, while DNMT3A, DNMT3B, and DNMT3L act on unmethylated DNA and are responsible for *de novo* methylation [24,25]. DNA demethylation involves the ten-eleven translocation family of enzymes TET(1–3) that convert 5mC to 5-hydroxymethylcytosine (5hmC) [26]. Additional epigenetic DNA modifications are known, however, their identification is technically more challenging and their function is less well studied [27–29]. Cancer development in general is associated with global DNA demethylation (hypomethylation) affecting intergenic regions, DNA repetitive sequences, gene bodies, including regulatory sequences; and aberrant *de novo* methylation of CpG islands (hypermethylation) in promoter regions of tumor suppressor genes [reviewed in [30]]. CpG islands refer to regions with high density of CpGs within a sequence and are often located in the regulatory region of promoters and are unmethylated in non-cancerous tissue [31]. Epigenetic gene silencing following CpG island methylation is mediated through methyl-CpG-binding domain (MBD) proteins such as MECP2 that recruit histone-modifying and chromatin-remodeling complexes to the methylated sites. DNA methylation profiles of cancer are highly characteristic and retain some traits of cell of origin. They have been successfully employed for re-defining/refining classification of brain tumors [12,32,33] or to determine the origin of metastasis of unknown primary cancer [34]. Most of the aforementioned studies reviewed here have been performed on the Illumina DNA methylation BeadChip platform that interrogates genome-wide DNA methylation and allows in addition gene copy number analysis. Hence, there are multiple efforts to develop molecular classifying algorithms based on data derived on the Illumina DNA methylation platform for WHO classification of brain tumors (e.g. The Heidelberg platform for next generation neuropathology can be used at: MolecularNeuropathology.org) [35]. Aberrant methylation of CpG islands in gene promoters leads to gene silencing affecting cancer relevant pathways associated with the hallmarks of cancer [36]. In glioblastomas activation of the WNT pathway is mediated by aberrant promoter methylation of multiple negative regulators, such as the gene encoding the WNT inhibitory factor 1 (WIF1) or the family of secreted frizzled-related proteins (sFRPs), dickkopf (DKK), and naked (NKDs) [37,38]. Similarly, negative regulators of the Ras pathway are silenced, such as the Ras association (RalGDS/AF-6) domain family member RASSF1A [39].

2.3. The glioma CpG Island methylator phenotype associated with IDH1 or IDH2 mutations

Gliomas with mutations in the metabolic genes *IDH1* or *IDH2* display a striking signature of DNA hypermethylation that is completely different from IDHwt gliomas, and has been termed Glioma CpG Island Methylator Phenotype (G-CIMP) [11]. This fairly recent discovery has indicated a novel driver mechanism in tumor development, consequently IDHmt gliomas are now considered a different disease as reflected in the WHO 2016 classification [17]. *IDH* mutations are early lesions in the development of gliomas and cluster in the substrate binding site of these enzymes, at codon 132 of *IDH1* or codon 172 of *IDH2*, respectively [40,41]. These mutations are always heterozygous and confer a gain of function that favors a neomorphic reaction catalyzing the conversion of α-ketoglutarate into D-2-hydroxyglutarate (2HG) [41]. 2HG acts as a so-called oncometabolite by accumulating to high concentrations that inhibit α-ketoglutarate-dependent enzymes. α-Ketoglutarate-dependent enzymes comprise epigenetic modifiers such as the enzyme TET2 involved in DNA demethylation or the lysine-specific histone demethylase KDM2A [28,29,42–45]. However, α-ketoglutarate-dependent enzymes are also involved in other cellular functions that are inhibited by 2HG, such as the DNA repair enzymes of the ALKBH family, thereby altering response to chemotherapy [46], or HIF1α regulating proteins, affecting hypoxia sensing/signalling [47]. Obviously, the cell metabolism is seriously disturbed. Respective vulnerabilities have been identified and proposed as treatment opportunities [45,48]. Similarly, acute myeloid leukemia (AML) display CIMP in presence of a mutation in *IDH1* or *IDH2,* with a preference for *IDH2,* or a mutation in *TET2*. These mutations are mutually exclusive, and