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.

KEYWORDS: Biomarker; Driver mutation; Epigenetic; Epigenetic drug; Glioma

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