Establishing a Robust Molecular Taxonomy for Diffuse Gliomas of Adulthood

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KEYWORDS

• Glioma • Glioblastoma • IDH1 • 1p/19q codeletion • Genomics • *TERT* • *ATRX*

ABSTRACT

The comprehensive molecular profiling of cancer has dramatically altered conceptions of numerous tumor types, particularly with regard to their fundamental classification. In the case of primary brain tumors, the widespread use of disease-defining biomarker sets is profoundly reshaping existing diagnostic entities that had been designated solely by histopathological criteria for decades. This review describes recent progress for diffusely infiltrating gliomas of adulthood, the most common primary brain tumor variants. More specifically, it details how routine incorporation of a handful of highly prevalent molecular alterations robustly designates refined subclasses of glioma that transcend conventional histopathological designations.

OVERVIEW

In their various forms, glial cells represent the most populous constituents of the central nervous system and exhibit characteristic histopathological features that have been extensively incorporated into the classification of brain tumors for decades. Not surprisingly, a broad spectrum of primary brain tumors exhibit morphologic features suggestive of glial histogenesis (**Box 1**). However, the precise term "glioma" has, over time, become inextricably associated with a defined group of diffusely infiltrating variants, most commonly seen in adulthood. Although these tumors feature considerable clinical and biological heterogeneity, their shared propensity for widespread invasion into surrounding normal brain, coupled with their notable refractoriness to conventional therapeutic approaches, effectively renders them uniformly incurable.

Gliomas are themselves segregated into distinct diagnostic entities on the basis of histopathological features thought to reflect the biological behavior of the tumors in question. Specifically, the current World Health Organization (WHO) classification system stratifies gliomas into 3 basic histiogenic lineages, astrocytic, oligodendroglial, and mixed (oligoastrocytic), while also arraying them across a spectrum of malignancy encompassing grades II, III, and IV (**Fig. 1**).[1] Within this schema, glioblastoma (GBM), WHO grade IV, represents that most aggressive variant, with a median survival of only 15 months in affected patients. By contrast, lower-grade gliomas (LGGs: astrocytomas, oligodendrogliomas, and oligoastrocytomas), ranging in WHO grade from II to III, are typically associated with more extended overall survival, even years to decades. Nevertheless, virtually all gliomas, regardless of grade at initial diagnosis, inexorably recur and progress, ultimately acquiring the histopathological features of glioblastoma, namely microvascular proliferation and necrosis (see **Fig. 1**). Accordingly, the term "secondary glioblastoma" has historically been applied in instances in which hallmark GBM histopathology emerges in the context of a lower-grade, predominantly astrocytic neoplasm.

In recent years, a series of large-scale molecular-profiling studies has greatly clarified the spectrum of genomic, and in some cases epigenomic, abnormalities occurring in the various glioma subtypes, and in doing so, dramatically altered conceptions of glioma pathogenesis. These developments have also prompted a fundamental rethinking of glioma classification. Although the current WHO system, outlined previously, performs quite well from the standpoint of prognostic stratification, it suffers from inherent interobserver variability. Moreover, as shown later in this article, highly recurrent molecular aberrations are now known to designate biologically distinct

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Surgical Pathology 9 (2016) 379–390
http://dx.doi.org/10.1016/j.path.2016.04.005

Box 1
Primary central nervous system (CNS) neoplasms with histopathological features of at least partial glial histogenesis

Primary glial neoplasms of the CNS

- Glioblastoma
- Astrocytoma
- Anaplastic astrocytoma
- Oligodendroglioma
- Anaplastic oligodendroglioma
- Oligoastrocytoma
- Anaplastic oligoastrocytoma
- Gliomatosis cerebri
- Pilocytic astrocytoma
- Pilomyxoid astrocytoma
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma
- Ependymoma
- Anaplastic ependymoma
- Myxopapillary ependymoma
- Subependymoma
- Astroblastoma
- Chordoid glioma of the third ventricle
- Angiocentric glioma
- Desmoplastic infantile astrocytoma/ganglioglioma
- Dysembryoplastic neuroepithelial tumor
- Ganglioglioma
- Anaplastic ganglioglioma
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor of the fourth ventricle
- Pituicytoma

disease subclasses that transcend conventional histopathological designations. This review describes how the comprehensive molecular characterization of glioma subtypes has reformed their taxonomy, impacting current clinical practice as well as the formulation of novel treatment strategies.

MUTATIONS IN ISOCITRATE DEHYDROGENASE GENES DISTINGUISH LOWER-GRADE GLIOMAS FROM GLIOBLASTOMA

Perhaps the most important insight gleaned from recent molecular profiling in gliomas is that primary GBMs fundamentally differ in their underlying biology and driving pathogenic mechanisms from LGGs and the secondary GBMs into which they evolve. This dichotomy is reflected most prominently by mutations in isocitrate dehydrogenase enzymes (IDH1 and IDH2), which have come to essentially define LGGs of adulthood. Ironically, point mutations in the *IDH1* gene were originally discovered in a study focused on primary GBM, among the first to use the unbiased approach of whole-exome sequencing.[2] The conjecture that *IDH1*-mutant tumors, approximately 11% of the sample cohort, might actually represent secondary GBMs led to subsequent investigations documenting strikingly high rates (70%–100%) of mutation in