Molecular genetics of oligodendrogliomas: a model for improved clinical management in the field of neurooncology

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Over the last several years, oligodendroglial tumors have become a model for the positive role of molecular genetics in improved treatment of patients with brain tumors. Oligodendrogliomas, in contrast to astrocytic gliomas, frequently respond to chemotherapy and have a better overall prognosis. Combined loss of chromosomes 1p and 19q has proven to be a powerful predictor of chemotherapeutic response and survival in oligodendrogliomas. In contrast, other genetic alterations, such as *TP53* and *PTEN* mutations, *EGFR* amplification, and homozygous deletion of *CDKN2A* have been correlated with worse outcome in these tumors. Furthermore, 1p/19q loss has been shown to correlate with unequivocal oligodendroglial tumor histology, location and growth pattern of tumors within the brain, and magnetic resonance imaging characteristics. Although much is also known about the molecular pathological characteristics of astrocytic gliomas, the significance of this information to clinical management in patients with these tumors has not been as striking as has been the case for oligodendrogliomas; possible reasons for this are discussed. In this paper the author will summarize these advances, thus attempting to highlight the molecular genetic study of oligodendrogliomas as a model for improved clinical management in the field of neurooncology.

KEY WORDS • oligodendroglioma • glioma • molecular genetics • chemotherapy • prognosis

Malignant gliomas are the most common primary brain tumors. These diffusely growing lesions have a distinct ability to invade the surrounding normal tissue, essentially preventing surgical cure. This phenomenon accounts for much of the high mortality rate associated with malignant glial tumors. To complicate matters, many of these tumors are resistant to standard therapeutic approaches. Nevertheless, glial lesions are extremely heterogeneous and some subtypes of diffuse glioma do in fact respond to therapy, thus highlighting the importance of proper classification.

The most widely used method of brain tumor classification is that of the WHO,⁵⁴ which is based on histological examination of the tumor tissue. The diffuse gliomas can be divided into one of three lineages according to histological appearance: astrocytoma, oligodendroglioma, and oligoastrocytoma. Oligodendroglial tumors are classified as such because they are considered to have a cellular morphology most closely resembling that of the normal oligodendrocyte. Briefly, oligodendrogliomas are characterized histologically by cells with round, uniform nuclei and peri-

nuclear halos (an artifact of standard tissue preparation), and often exhibit delicate, branching vessels as well as calcification. The WHO classification system also assigns a tumor grade to glial lesions. Grade II is the lowest grade given for malignant oligodendroglioma. Grade III (anaplastic) oligodendrogliomas are more densely cellular than Grade II tumors, and are distinguished from Grade II lesions by the observation of brisk mitotic activity. Anaplastic oligodendrogliomas can also exhibit vascular proliferation and/or necrosis. Grade III is the highest grade given to oligodendrogliomas.

In the majority of cases, the WHO classification system can be used successfully to assign tumors to specific, relevant categories. Nevertheless, pathological diagnosis remains quite subjective,⁶⁴ leading to some inadequacies in the current system. For example, intratumoral histological variability can make it difficult to place some gliomas neatly into one of the defined categories. Moreover, high-grade gliomas may exhibit little cellular differentiation, thereby lacking defining histological features. The diagnosis of tumors with such nonclassic histological features can therefore be controversial. Furthermore, tumor grading can be difficult when only tissue from small stereotactic biopsy samples is available for examination.³⁴ Consequently, diagnosis of glial tumors can be challenging, and the resulting

Abbreviations used in this paper: CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CGH = comparative genomic hybridization; EGFR = epithelial growth factor receptor; MR = magnetic resonance; PCV = procarbazine, CCNU, and vincristine; WHO = World Health Organization.

interobserver variability can jeopardize diagnostic accuracy and reproducibility.^{23,33} Furthermore, even when a histological diagnosis is virtually indisputable, the corresponding predicted clinical behavior does not always concur with the patient's actual clinical course. Moreover, it is unlikely that the current WHO classification system alone will accurately predict patient response to novel targeted molecular therapies as they become available in the future. For these reasons, information capable of refining the WHO system could result in marked improvements in the current approach to brain tumor classification and, subsequently, aid the clinical management of gliomas. To this end, advances in molecular genetics have revolutionized the classification and clinical management of one subtype of malignant glioma, anaplastic oligodendrogliomas. In this paper I will review some of these advances, many of which are summarized in Fig. 1, with the goal of highlighting the promise of this approach as a model for improved clinical management in neurooncology as a whole.

Molecular Genetics of Oligodendroglial Tumors

The most common genetic alteration in oligodendrogliomas is the combined allelic loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), affecting 50 to 90% of tumors.^{7,8,55,85,109} These chromosomal losses are detected in Grade II as well as Grade

III lesions, suggesting an early role in oligodendroglial tumorigenesis. The fact that losses of chromosome 1p and 19q are closely correlated implies that the corresponding putative tumor suppressor genes may be involved in biologically distinct pathways that act synergistically in oligodendroglial tumorigenesis.^{7,40,55,85} Mapping of these chromosome loci has implicated the telomeric region of 1p and 19q13.^{3,27,30,37,43,55,90,97,100,120} In the search for potential oligodendroglial tumor suppressor genes within the regions of 1p and 19q loss, examples of commonly mutated genes have not been forthcoming. Therefore, a number of laboratories have begun to focus on possible alternative genetic and epigenetic mechanisms for modulating gene expression, including polymorphisms and methylation.^{1,25,26,41,105,118,119}

Additional genetic alterations found commonly in anaplastic oligodendrogliomas include allelic losses of chromosome 9 involving the *CDKN2A* gene, and chromosome 10.^{9,10,18,40,46,92,104} Homozygous deletions of *CDKN2A* on 9p21 occur in up to one third of anaplastic oligodendrogliomas.⁴⁰ Both 9p and 10q aberrations are more common in tumors without 1p/19q loss.^{18,40,46} Disruption of the cell cycle through the RB1/CDK4/p16^{INK4a}/p15^{INK4b} and the p53/p14^{ARF}/MDM2 pathways is common in anaplastic oligodendrogliomas,^{9,115,118} with simultaneous disruption of these two pathways suggested to occur in approximately half of

Fig. 1. Flow charts summarizing key clinical features correlated with 1p loss in oligodendroglial tumors (see text for details). "Other" defined genetic alterations include *TP53* mutation, 10q loss, *PTEN* mutation, *EGFR* amplification, or deletion of *CDKN2A*. T1 = T₁-weighted MR imaging.

the tumors.¹¹⁵ In particular, hypermethylation may be an important epigenetic mechanism by which oligodendrogliomas escape such cell cycle control.^{26,114,115,118}

Oncogene amplification has rarely been found in oligodendroglial tumors, most commonly affecting *EGFR*, *PDGFRA*, and *CDK4*.^{31,84,101} A number of other less common chromosomal aberrations have been demonstrated in oligodendrogliomas^{9,11,24,48,52,56,88,89} and, with increasing numbers of high-resolution array-based CGH studies being performed,^{11,24,52,88,89} these data are expected to yield better boundary definition for the discovery of potential novel genes involved in oligodendroglial tumorigenesis. Moreover, gene expression-based microarray and proteomic analyses are also providing massive quantities of molecular genetic data to be mined for insights into tumorigenesis in oligodendroglioma.^{32,42,47,51,73,75,116}

Response of Oligodendrogliomas to Chemotherapy and the Predictive Value of Molecular Genetics

Historically, although diffuse gliomas were classified into diagnostic subgroups, this made little difference in the clinical management of these lesions; all patients with malignant gliomas were treated according to standardized treatment protocols regardless of whether they had an astrocytic or oligodendroglial tumor. This approach began to shift in 1988, when it was first reported that recurrent anaplastic oligodendrogliomas sometimes displayed a marked response to the chemotherapeutic regimen of PCV.¹⁷ This was quickly followed up by a report in 1990 confirming that newly diagnosed anaplastic oligodendrogliomas also responded to PCV therapy.⁶⁷ Subsequently, low-grade (WHO Grade II) oligodendrogliomas and oligoastrocytomas were also found to respond favorably to chemotherapy.^{35,50,58,68} Furthermore, oligodendroglial tumors have also been shown to respond to temozolomide,^{22,106,107} a newer chemotherapy drug that can be taken orally and is often better tolerated by patients.

The most significant example to date of molecular genetics aiding the clinical management of malignant gliomas is the use of 1p/19q testing to predict the response of oligodendrogliomas to chemotherapy. Allelic loss of chromosome 1p in anaplastic oligodendrogliomas has proven to be a powerful predictor of tumor response to PCV treatment.^{18,46,98} Loss of 1p also appears to predict the response of anaplastic oligodendrogliomas to temozolomide as well as that of low-grade oligodendrogliomas to chemotherapy.^{15,20,39,91} Furthermore, the combined loss of 1p and 19q predicts longer survival in patients with anaplastic oligodendroglioma,^{18,46,69,98,112} even after recurrence.²⁹

Currently, molecular genetic analyses can be used to divide anaplastic oligodendrogliomas into four therapeutically and prognostically relevant subgroups⁴⁶ (Fig. 1). Briefly, anaplastic oligodendrogliomas displaying combined loss of 1p and 19q in the absence of additional defined genetic alterations respond to chemotherapy in a durable manner, thereby resulting in a mean patient survival of more than 10 years. Oligodendroglial lesions with loss of 1p in the absence of 19q loss, or tumors that have 1p/19q loss in the presence of additional genetic alterations, also respond to chemotherapy, but their response is less durable and patient survival is shorter. In contrast, two additional molecular subgroups exist in the absence of 1p loss and are distin-

guished based on the presence or absence of p53 mutation; these oligodendrogliomas respond to chemotherapy less frequently and are associated with a more aggressive clinical outcome. Thus, these data demonstrate how molecular genetic analyses could be used to aid treatment decisions from the time of diagnosis. For example, patients exhibiting 1p/19q loss in the absence of other genetic alterations might forgo radiation therapy until recurrence, thereby avoiding the side effects attributed to brain irradiation in long-term survivors. In contrast, patients with tumors belonging to the fourth genetic subgroup, the one least likely to respond to chemotherapy, may choose radiation and/or a novel therapy as their primary treatment strategy. Moreover, loss of 1p has been demonstrated to be predictive of response to radiation.⁶

A number of additional genetic alterations have been correlated with prognosis in oligodendrogliomas. Mutation of p53 and loss of chromosome 10q have both been linked to poor prognosis,^{18,40,46,70,92,103,112} as has allelic loss of 9p21, or more specifically, deletion of the *CDKN2A* gene.^{18,70} All of these genetic alterations have been shown to have a negative correlation with 1p/19q loss in oligodendrogliomas.^{18,40,46,69,112}

Correlation of Molecular Genetics With Clinical Diagnostic Methods

Correlation With Oligodendroglial Histological Features. As mentioned in the introductory section, one of the shortcomings of histology-based diagnoses is that the diagnosis of tumors with nonclassic histological features can be controversial. Using a high-throughput molecular genetics approach to address this issue, the power of a gene expression-based prediction model to aid the classification of high-grade gliomas was recently demonstrated.⁷⁵ In that study, supervised learning approaches were used to build a two-class model to separate a subset of anaplastic oligodendrogliomas and glioblastomas with “textbook” histological features. This two-class model was then used to predict a classification for a series of high-grade gliomas with nonclassic histological features. Because patients with anaplastic oligodendrogliomas experience a significantly longer average survival time than those with glioblastomas,^{54,77} survival was examined as an independent validation of the gene expression-based prediction model; classification based on expression profiling provided stronger outcome prediction than did classification based on standard pathological studies.

These data provided evidence that microarray-based classification may be better suited to distinguish between anaplastic oligodendrogliomas and glioblastomas in a clinically relevant manner. Subsequently, in an effort to develop an immunohistochemical panel capable of distinguishing between these two classes of tumors, a number of differentially expressed genes from the microarray study were confirmed at the protein level. One molecule, YKL-40, was highly expressed in glioblastomas compared with anaplastic oligodendrogliomas, and it was determined that immunohistochemical staining of YKL-40 alone could distinguish these tumors in a highly significant manner.⁷⁴

In addition to correctly identifying oligodendrogliomas during the initial diagnosis, the therapeutic significance of subsequently testing these lesions for 1p/19q loss was clear-

<p><u>Classic Low Grade Oligodendroglioma Features</u></p> <ul style="list-style-type: none"> - uniform and rounded nuclei, often with small nucleoli - perinuclear halos - even cellular distribution within tissue - calcification and “chickenwire” vasculature (informative but not required) <p><u>Low Grade Oligodendroglioma Astrocytic Features</u></p> <ul style="list-style-type: none"> - mildly pleomorphic, more hyperchromatic nuclei - tapering eosinophilic cell processes - irregular cellular distribution within tissue

Fig. 2. Chart detailing histological features of classic low-grade oligodendrogliomas and low-grade oligodendrogliomas with astrocytic feature (see Sasaki, et al., 2002).

ly evident. In light of this fact, more neuropathologists began to perform 1p/19q testing in their histologically diagnosed oligodendrogliomas. Interestingly, some of these practitioners began to recognize histological features that distinguished tumors with 1p/19q loss from those with intact chromosomal 1p/19q. In one study, Burger, et al.,¹² reviewed 18 classic and borderline cases of infiltrating glioma. Of six cases diagnosed unanimously as oligodendroglial lesions, all had allelic loss of 1p and 19q. Interestingly, none of these six tumors had *TP53* mutations. In contrast, nine cases were assigned an astrocytic classification on review; all demonstrated intact 1p alleles and three exhibited *TP53* mutations (*TP53* status was not available in two of the nine cases). Notably, six of these nine tumors had been categorized as oligodendroglioma or mixed glioma by the referring institutions.

In a study by Ueki, et al.,¹⁰⁴ eight cases in a larger, nonselected series were diagnosed unanimously as oligodendrogliomas by four independent neuropathologists; one of these tumors had 19q loss but was noninformative for 1p status, and all of the remaining seven lesions demonstrated 1p/19q loss. In contrast, *TP53* mutation was detected most often in tumors with astrocytic features. Furthermore, Sasaki, et al.,⁹¹ selected a series of 44 low-grade oligodendrogliomas and divided the cases into two groups: classic oligodendroglioma and lesions with astrocytic features. The histological features used to classify tumors into each of these two groups are given in Fig. 2. Loss of 1p was observed in 86% of the classic oligodendrogliomas, whereas 73% of the oligodendroglial tumors with astrocytic features retained both allelic copies of 1p. Thus, it appeared that glial tumors with 1p/19q loss were the most likely to demonstrate an unequivocal oligodendroglial histology, regardless of tumor grade, whereas mutated p53 was associated with the presence of astrocytic histological features. Moreover, McDonald, et al.,⁶⁹ demonstrated that defining oligodendrogliomas with classic histological features in this manner yielded prognostic predictability similar to that provided by 1p/19q loss.

The aforementioned studies give examples of how molecular genetics can aid histology-based classification of glial tumors. Nevertheless, because the current method of tumor specimen management in pathology departments worldwide makes use of formalin-fixed, paraffin-embedded tissues, immunohistochemistry is routinely used to aid

diagnosis. Unfortunately, no immunohistochemical markers currently exist that exclusively stain oligodendrogliomas. As noted earlier, gene expression-based data have been used to develop a new immunohistochemical marker capable of labeling glioblastomas relative to anaplastic oligodendrogliomas.^{74,75} A number of laboratories are currently using this microarray-based approach in an attempt to identify oligodendroglioma-specific markers. With the ever-increasing numbers of gene expression-based and proteomic studies being performed,^{32,42,47,51,73,75,116} it is hoped that such clinically relevant oligodendroglial markers will be forthcoming in the future.

Correlation With Tumor Location and Pattern of Growth. Although initial molecular genetic studies in oligodendroglioma focused on correlations with clinical outcome, studies in which biological properties were investigated have begun to emerge. Zlatescu, et al.,¹²¹ demonstrated that anaplastic oligodendrogliomas with allelic loss of 1p and 19q were significantly more likely to be situated in the frontal, parietal, and occipital lobes of the brain. In contrast, oligodendroglial tumors with intact 1p and 19q alleles, although histologically indistinguishable from lesions found in the frontal, parietal, and occipital lobes, arose more often in the temporal lobe, insula, and diencephalon.^{69,121} Similarly, most temporal oligoastrocytomas have also been found to have intact 1p and 19q alleles.⁷² In contrast to oligodendrogliomas, however, temporal oligoastrocytomas tended to exhibit more astrocytic histological features than those found in other areas of the brain and were often accompanied by p53 mutation. No association between molecular genetics and location has been established in astrocytic tumors. These findings raise the interesting question of whether different subtypes of oligodendroglial tumors might arise from different progenitor cells that are localized to specific regions of the brain or that appear at different stages of development.¹²¹

Beyond location of oligodendrogliomas, 1p and 19q status has also been linked to the pattern of growth of these lesions. Based on the clinical observation that oligodendrogliomas in deeper regions of the brain were more often well circumscribed on MR imaging and grew as expansive rather than infiltrative masses, Zlatescu, et al.,¹²¹ investigated whether allelic loss of 1p and 19q correlated with the manner in which these oligodendrogliomas grew within the brain. In a series of 64 tumors, lesions in seven patients dis-

played a bilateral rather than a unilateral pattern of growth; all of these oligodendrogliomas with bilateral growth demonstrated 1p/19q loss. The possibility that oligodendrogliomas with 1p/19q loss grow in a more infiltrative manner raises the additional hypothesis that this particular genetic alteration facilitates a distinct interplay with the extracellular environment. Clearly, because both the cell of origin for subtypes of oligodendrogliomas and the interaction that these lesions have with their environment could have profound implications for the clinical management of these tumors, additional investigations into the biological consequences of 1p/19q loss are certainly warranted.

Correlation With Oligodendroglioma Imaging. Clinical management of malignant gliomas is highly dependent on MR imaging findings. Because of this, it is not surprising that the most recent advancements in the study of oligodendrogliomas have resulted from investigating possible correlations between 1p/19q status and imaging characteristics. Again suggestive of a more infiltrative growth pattern for oligodendrogliomas with 1p/19q loss, tumors with this genotype were more likely to demonstrate an indistinct border on T₁-weighted MR images. In contrast, oligodendroglial lesions with intact chromosomal 1p and 19q tended to display sharper borders on MR imaging⁷¹ and sometimes displayed ring enhancement.¹⁸ Oligodendroglial tumors with 1p/19q loss were also more likely to exhibit mixed signal intensity. Moreover, this signal heterogeneity, along with susceptibility change, correlated with the presence of intratumoral calcification in oligodendroglial tumors exhibiting 1p/19q loss, although the association between intratumoral calcification and susceptibility effects is likely to be indirect. Furthermore, tumors with 1p/19q loss have also been associated with a hypermetabolic state, particularly in patients with low-grade oligodendrogliomas.^{16,111} Intriguingly, these data highlight the potential for methods of imaging-based molecular diagnostic modalities in the future.

Role of Molecular Genetics in Clinical Management of Astrocytic Tumors

Analogous to oligodendrogliomas, much is known about the molecular genetics of astrocytic tumors.^{44,53,63,76,79,83,94} Glioblastomas, the most malignant astrocytic tumor, can generally be divided into two groups based on molecular analyses: those with *TP53* mutation and those with *EGFR* amplification.^{54,65,110} Secondary glioblastomas, lesions that have arisen in a background of prior lower-grade astrocytoma, are often p53-mutated tumors, but p53 mutations can also be found in glioblastomas with no history of glioma.^{86,110,113} Tumors with *EGFR* amplification, however, are characteristic of primary, or de novo, glioblastomas.^{110,113} Glioblastomas with mutated p53 tend to occur in patients younger than those in whom the lesions are characterized by *EGFR* amplification,^{66,82} and young age at initial diagnosis is an important predictor of better outcome in these tumors.

A number of studies have been conducted to examine the independent prognostic implications of p53 mutation and *EGFR* overexpression or mutation,^{5,14,38,93,95,96,99} but much of this information implies that the relationship between age, p53 mutation, *EGFR*, and survival in astrocytic gliomas is rather complex. In one study, patients with glioblastoma

were initially differentiated based on length of survival; nuclear expression of p53 was detected more frequently in long-term survivors, whereas overexpression of *EGFR* appeared to be slightly more common in short-term survivors.¹⁴ In comparison, when patients with glioblastoma were differentiated based on age, *EGFR* overexpression correlated with poor prognosis only in younger patients; older patients with overexpression of *EGFR* actually had a better prognosis.^{95,96,99} Moreover, among patients with glioblastoma who were younger than the median age, overexpression of *EGFR* was related to a shorter survival time in those with wild-type p53 but not in those whose tumors stained positively for p53 in an immunohistochemical study.⁹⁶ In addition, *EGFRvIII*, a mutant form of *EGFR*, has been implicated as a predictor of unfavorable prognosis in patients surviving more than 1 year.³⁸ The prognostic effects of p53 also appear to be dependent on the age of the patient.⁵

Another genetic alteration that has been associated with prognosis in astrocytic tumors is the allelic loss of chromosome 10q. Loss of 10q is the most frequent genetic alteration in glioblastomas,^{45,49,77,81,108} and has been associated with a low survival rate.^{77,80,93,102} Furthermore, mutation of *PTEN*, a 10q gene, has also been correlated with poor prognosis.^{28,99} Additional molecular markers predicting a negative prognosis for patients with astrocytic gliomas have included the following: loss of chromosome 9p or *CDKN2A* deletion,⁸⁰ gains of 7p and 7q,⁵⁷ activated phosphatidylinositol 3-kinase,²¹ YKL-40,⁷⁸ and a dysfunctional RB pathway.² Furthermore, CGH^{13,57,117} and gene expression profiling^{62,87} have also provided novel sources of prognostic information.

The predictive value of molecular genetics for determining treatment response has met with less success for astrocytic gliomas than for oligodendrogliomas. There has been some evidence for a correlation between *EGFR* overexpression and resistance to radiation,^{4,59-61} although much of this information has been obtained from in vitro studies.⁵⁹⁻⁶¹ The YKL-40 molecule has also been implicated as a marker of radioresistance.⁷⁸ Most recently, *EGFR* status has been investigated in astrocytic gliomas treated with erlotinib, a small-molecule inhibitor of *EGFR*. One study demonstrated that tumors with high levels of *EGFR* expression and low levels of phosphorylated PKB/Akt responded better to erlotinib than lesions with low levels of *EGFR* and high levels of phosphorylated PKB/Akt.³⁶ Nevertheless, six of the 10 patients with *EGFR* amplification did not respond to erlotinib, suggesting that this agent may be active only in a subset of gliomas with *EGFR* expression.^{19,36}

CONCLUSIONS

Malignant gliomas are the most lethal of brain tumors. Much progress has been made in the treatment and prognosis of one subtype of glioma in particular, the anaplastic oligodendroglioma. In this paper I have attempted to highlight the role of molecular genetics in the improved clinical management of oligodendroglial tumors. Although much is also known about the molecular pathological characteristics of astrocytic gliomas, the significance of this information to the clinical management of these tumors has not been as striking as it has been for oligodendrogliomas. A number of reasons exist for this observation. First, patients

with astrocytic tumors, particularly glioblastomas, have a much shorter survival time than individuals with oligodendroglial lesions; the median survival duration for patients with glioblastomas is less than 1 year,⁵⁴ making it very difficult to stratify them to a degree meaningful enough for the development of prognostic markers. Similarly, the key reason for the success of 1p testing in patients with oligodendroglomas was the marked response these tumors demonstrated to PCV chemotherapy; such highly effective treatments are not currently available for astrocytic tumors, hindering the development of response markers.

The recent emphasis on the development of targeted molecular therapies affords the possibility of more effective treatment options for nervous system tumors in the near future. This is made all the more exciting by the plethora of novel data coming out of studies in which methods such as array-based CGH and gene expression profiling are being used; these studies will greatly expand the number of potentially informative molecular markers. Therefore, it is hoped that the progress made in oligodendroglial tumors can serve as a model for improved clinical management through the use of molecular genetics, leaving the field of neurooncology poised to take advantage of these approaches when more effective treatments become available, not only for astrocytic gliomas but for nervous system tumors in general.

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