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Special Article

Glioma Classification

A Molecular Reappraisal

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The modern clinical practice of neuro-oncology is dependent on accurate tumor classification. No variable predicts prognosis more precisely, and classification is also the basis on which clinicians make critical therapeutic recommendations to their individual patients: neuro-oncologists apply therapies in a relatively uniform way for all patients with a given tumor type. Hence, in a profound way, treatment of brain tumors is dictated by histological diagnosis. Furthermore, classification guides our scientific study of brain tumors, with biological understanding often based on *a priori* assumptions about specific tumor types. In the future, as specific therapies become based on individual biological alterations within tumors, precise classification will assume even greater importance to guide these distinct treatments. The primacy of accurate classification in neuro-oncology demands that critical attention be directed toward the problem, and encourages periodic re-evaluations of this essential issue.

The present reappraisal is directed toward the diffuse gliomas. These are the most common of primary human brain tumors and comprise the bulk of adult neuro-oncology work. Diffuse gliomas are therapeutically vexing: their infiltrative (diffuse) growth pattern essentially prevents surgical cure, and the majority of these gliomas are resistant to standard chemotherapeutic and radiotherapeutic approaches. Nonetheless, some tumors are therapeutically sensitive and rare cures are effected. Paradoxically, these rare successes draw attention to the essential limitation of current glioma classification schemes: responding tumors may be histologically indistinguishable from nonresponding ones.

Consequently, existing methods of glioma classification fall short of their ultimate goal of precisely guiding therapy. However, molecular biological studies of gliomas are making inroads toward an improved classification system for gliomas, one in which response to a specific therapy can be predicted for each individual patient. Furthermore, remarkable insights into the origins and behavior of gliomas are beginning to emerge from animal modeling of glial tumors and from basic research in developmental neurobiology. Together, such scientific advances and therapeutic successes provide an opportunity to question and perhaps refine the paradigm for classifying diffuse gliomas.

The present reappraisal first defines the problems inherent in current glioma classification systems. Next, by reviewing advances in our molecular understanding of gliomas, we suggest that a more biological approach to glioma classification will provide improved means to type these tumors. Any new classification, however, must be based on clinical significance, and we thus point out the pressing need for better clinical endpoints and outcome measures in the field. Finally, by looking at basic advances in developmental neurobiology and animal modeling, we raise the possibility that we should begin to think of gliomas in a different conceptual framework. In combination, these data suggest that the present is an opportune time to begin to reconsider how glioma classification should advance during the next few years.

The Problem: Current Glioma Classification

Most of the current glioma classifications are derived from the seminal system of Bailey and Cushing.[1] Bailey and Cushing, rather presciently for the 1920s, drew parallels between the histological appearances of glial tumors and putative developmental stages of glia. Thus, they reasoned that the cells of astrocytomas microscopically most closely resembled astrocytes and those of oligodendrogliomas histologically most mimicked oligo-

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WHO II	astrocytoma (3-10 yrs; ? %)	oligo-astrocytoma (5-12 yrs; ? %)	oligodendroglioma (8-20 yrs; ? %)
WHO III	anaplastic astrocytoma (2-5 yrs; 10-30%)	anaplastic oligo-astrocytoma (2-8 yrs; 20-60%)	anaplastic oligodendroglioma (2-10 yrs; 40-80%)
WHO IV	glioblastoma (1-2 yrs; 10%)		

Figure 1. Limitations of the current World Health Organization classification of diffuse gliomas for estimating prognosis and guiding therapy. **Left:** World Health Organization grades are indicated. Under each tumor type are the range of typical survival (in years) and frequency of response to therapy (in percentages). ?, Percentages for World Health Organization grade II lesions are uncertain; radiographic responses tend to be modest, but may not be indicative of biological response.

dendrocytes. As these tumors became more malignant, they resembled less differentiated (ie, earlier) precursor cells; hence, malignant astrocytomas were dubbed "astroblastomas." Some of these seminal concepts were confirmed during the latter half of the twentieth century. For instance, both at the ultrastructural level and at the immunohistochemical level, many astrocytomas are comprised of cells that exhibit astrocytic differentiation. Whether the cell of origin of a glial tumor can be inferred from its differentiation, however, is unclear. Indeed, the specific cells of origin for gliomas remain enigmatic.

The most widely used current classification of human gliomas is that of the World Health Organization, revised in 2000.[2] The 2000 World Health Organization system divides diffuse gliomas into astrocytic tumors, oligodendrogliomas, and oligoastrocytomas. These are then graded into histological degrees of malignancy. Oligodendrogliomas and oligoastrocytomas are tiered into grade II and anaplastic, grade III lesions. The astrocytomas include grade II, grade III, and grade IV lesions, with grade IV known as glioblastoma (Figure 1).

For the most part, the 2000 World Health Organization classification system is a practical and effective approach to brain tumor analysis. In the vast majority of cases, it provides a means for placing tumors into specific, relevant categories. But classification schemes that are based on visual criteria alone are, by definition, subjective, and allow considerable interobserver variation.[3] In addition, traditional groupings are only satisfactory for series of cases, and not necessarily adequate predictors of behavior, response to therapy or survival for individual tumors and patients (see Ranges of Survival and Response in Figure 1). Some diffuse gliomas are also difficult to place neatly into one of the World Health Organization categories, which can result in diagnostic waffling, or nebulous diagnoses such as "malignant glioma, not otherwise specified." Alternatively, in difficult differential diagnoses, pathologists may feel under pressure to make certain diagnoses so that clinicians do not overlook specific therapeutic options for their patients. In other situations, the histological diagnosis and corresponding predicted clinical behavior do not match the actual clinical course. In a significant number of situations, therefore, standard histological classification is not effective.

Looking forward, it is also unclear whether the current histopathological system will correctly predict patient course once truly effective therapies are developed, particularly if such therapies become more mechanism-based. Even today, in the case of anaplastic oligodendroglioma, for which existing treatment can be highly effective, histological examination does not provide a good method of distinguishing chemosensitive from chemoresistant tumors.[4–6] These problems clearly indicate room for improvement in the current approach to glioma classification. In this regard, we believe that a classification for gliomas that is based on tumorigenic mechanisms has a greater likelihood of achieving universal clinical relevance; whereas a simple "rearranging of deck chairs" will not be particularly helpful.

Improving Classification: Molecular Approaches

The discovery that cancer is a genetic disease, arising when defects occur in growth-regulatory genes, has revolutionized our understanding of tumorigenesis. Inquiries into the genetic basis of gliomas have yielded large amounts of information about specific genetic events that underlie the formation and progression of human gliomas.[2,7] Specific molecular alterations are associated with astrocytic gliomas, and other genetic changes with oligodendrogliomas. Significantly, however, particular genetic changes may occur in some astrocytomas and not in others, or in only some oligodendrogliomas, hinting that there may be molecular subtypes of histologically defined astrocytoma or oligodendroglioma. Given the likely biological differences occasioned by such genetic variety, it would not be surprising to learn that each subtype requires a specific and unique set of treatments.

For glioblastomas, genetic subsets have been defined, for instance on the basis of mutually exclusive *TP53* and *EGFR* gene alterations: *EGFR* gene amplification almost never occurs in those glioblastomas with *TP53* mutation or allelic loss of chromosome 17p.[8–13] The glioma pathway that includes *TP53* inactivation is characteristic of (but not restricted to) glioblastomas that have arisen in younger adults through malignant progression from a lower grade astrocytoma—so-called "secondary glioblastoma."[10,14,15] Those glioblastomas with *EGFR* amplification, on the other hand, most often occur in older patients with a short clinical history and no definite previous lower grade astrocytoma—so-called "primary glioblastoma."[10] The correlation of genetic alterations with patient age is of great clinical interest, because age is one of the most powerful determinants of clinical course in patients with glioblastomas.[16] The ability of molecular genetics to detect biological heterogeneity in glioblastomas raises the possibility that new approaches to glioma classification could be based on objective biological parameters. It also raises the possibility that the rare glioblastoma that is cured by current therapeutic maneuvers has a specific genetic signature that we could learn to recognize.[5]

For anaplastic oligodendrogliomas, the therapeutic relevance of molecular subtyping is already apparent (Figure 2).[4,6,17] In these tumors, combined chromosomal losses of 1p and 19q are inversely related to allelic losses of chromosomal arms 9p, 10q, and 17p and respective

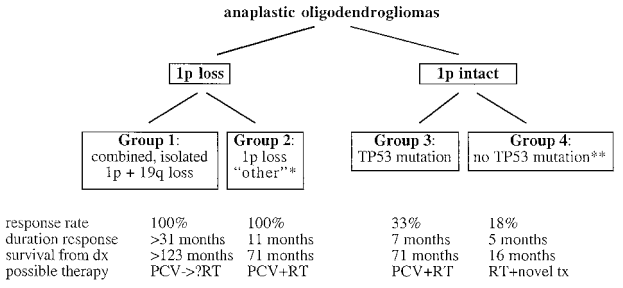

Figure 2. Anaplastic oligodendroglioma: an example of molecular approaches to glioma classification (adapted from Ino et al[4]). Four genetic subgroups of World Health Organization grade III anaplastic oligodendrogliomas have differences in response frequency, duration of response, and survival. *, Group 2 patients have 1p loss, but either do not have 19q loss or have other genetic alterations such as TP53 mutation, PTEN mutation, 10q loss, EGFR amplification, or CDKN2A deletion. **, Group 4 patients often had PTEN mutation, 10q loss, EGFR amplification, CDKN2A deletion, and ring enhancement. dx, Diagnosis; PCV, chemotherapy (see text); RT, radiation therapy; novel tx, novel therapy.

inactivation of the *CDKN2A*, *PTEN*, and *TP53* genes.[18–23] Anaplastic oligodendrogliomas are distinguished by their remarkable chemosensitivity to procarbazine, lomustine (CCNU), and vincristine chemotherapy (PCV).[24–26] Although no clinical or pathological feature predicts response correctly, allelic loss of chromosome 1p is a powerful predictor of chemotherapeutic response,[4,6] and combined losses of 1p and 19q are strong predictors of longer survival.[4,6,17] Such data imply that the differential clinical behaviors reflect two independent biological subtypes of anaplastic oligodendroglioma that express a different repertoire of genes. These observations suggest rather strongly that molecular genetic analyses may eventually guide therapeutic decisions for patients with types of malignant glioma that are more common and more aggressive than oligodendrogliomas. As discussed above, it is well known that occasional anaplastic astrocytomas and glioblastomas respond to current therapies, although it has not been possible to identify such cases in advance of therapy.[5]

Molecular diagnostic approaches to brain tumor classification have therefore already made practical inroads. We recommend clinical testing for chromosome 1p loss in patients diagnosed with anaplastic oligodendrogliomas, as well as for selected patients with grade II oligodendrogliomas for whom therapeutic decisions might be influenced by additional knowledge of probable tumor behavior. For example, chemotherapy might be an alternative to radiotherapy as the initial adjuvant treatment for a symptomatic enlarging grade II oligodendroglioma with 1p loss that is no longer amenable to surgical resection; whereas radiotherapy might be preferable for such a tumor if 1p loss is not present. Testing for 19q loss, as well as 10q loss, *CDKN2A/p16* deletion, *EGFR* gene amplification, and *TP53* mutation also provides useful information,[4] but each test adds to the time and expense of the clinical laboratory effort. Indeed, for us, the modern clinical management of oligodendrogliomas requires the neuro-oncologist to consider a combination of different parameters: clinical features, histopathological grade, MIB-1 proliferation index, tumor genotype, and neuroimaging findings. For glioblastomas, on the other hand, analysis for *TP53* mutations and *EGFR* gene amplification currently has no definite prognostic or therapeutic relevance, and there is therefore no current clinical need for such tests. Nonetheless, as discussed below, such analysis should be built into clinical trial work, even at the present time.

To date, molecular subtyping approaches have been primarily genomic—focusing on the relatively few, but presumably causal, tumorigenic events. The advent of expression profiling furthers the eventual reality of a mechanism-based classification by expanding the number of molecules that can be assayed and by shifting emphasis to expressed molecules.[27,28] Although such approaches are currently focused on use of cDNA microarray technologies, proteomic-based profiling would highlight the actual molecules effecting the neoplastic phenotype. Most likely, the clinical behavior of neoplasms—their rates of growth and their responses to therapy—will be related to specific protein pathways that are activated or inactivated in each subtype of tumor.

Improving Measures of Clinical Significance: The Need for Novel Endpoints and Outcomes

For a few kinds of primary brain tumor—such as benign, resectable tumors and rare chemosensitive and/or radiosensitive neoplasms—cure is possible. Primary central nervous system malignant lymphomas, for example, sometimes respond dramatically and durably to chemotherapy. But, for the diffuse gliomas, patient care and clinical research in neuro-oncology throughout the past many decades have been geared toward gradually prolonging the lives of patients, with length of survival being the most important indicator of a treatment effect. Implicit in this approach has been the assumption that diffuse gliomas are relatively homogeneous diseases and that survival times can gradually be increased as a result of continuous refinement of existing therapies, while searches continue for truly effective treatments. This assumption, however, discounts the likely possibility that each histological subtype of glioma comprises many diseases, each requiring unique and different therapeutic tools. Our current clinical research strategy of improving survival would dismiss as ineffective a therapy that helped 50% of cases and worsened 50% because no aggregate change in survival would be detected. A triage strategy based on an early correct assessment of response would be a more logical approach, especially when there are multiple diseases to be treated and multiple new therapies to test. In this regard, response assessment should also occur in the context of molecular characterization of the tumor. With such information, we would begin to build bridges between treatment effects and basic biology (Figure 3).

Unfortunately, for the near future, glioma research will be handicapped by the paucity of endpoints and outcome measures that provide immediate feedback on the utility of a given therapy. Modern neuroimaging holds promise for providing new outcome measures, by allowing measurements of tumor response to therapy that may

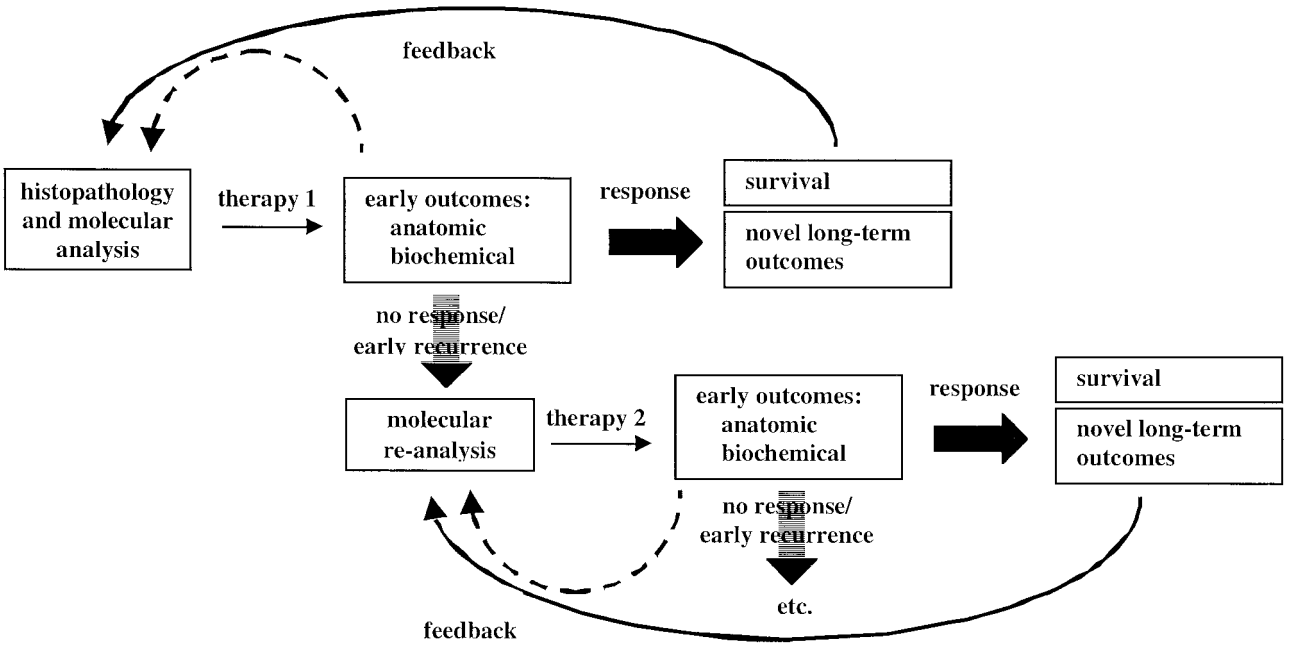

Figure 3. The need for novel endpoints. Currently, survival provides the major endpoint for guiding subsequent changes in histological classification (see text). In the future, early alternative endpoints will be necessary to provide immediate therapeutic guidance (**curved dashed arrows**) in the setting of nonresponse to a particular therapy and for eventually refining molecular classifications. In addition, novel long-term outcome measures will be needed to further refine classification and thus indirectly guide subsequent therapy (**curved solid arrows**). The eventual goal is for molecular subtyping to determine different specific therapies.

be independent of patient survival. However, change in tumor size on neuroradiological examination, the usual current measure of response, is a crude measure and is almost certainly an insufficient gauge of anti-glioma activity. As a result, surrogate markers measured by neuroimaging or in fluids such as serum or cerebrospinal fluid would be important additions to the field. For instance, following of markers such as alpha-fetoprotein (AFP) in germ cell tumors helps to follow patient response to therapy and provides a window on tumor recurrence, in a manner more sensitive than available by neuroimaging. No such markers have been validated to date for the diffuse gliomas.

The identification of surrogate markers is therefore a high priority in neuro-oncology (Louis DN, Posner JB, Jacobs T, Kaplan R: Report of the Brain Tumor Progress Review Group. http://ospncinihgov/prg_assess/prg/btprg/, 2000). There may be biological differences, for instance, between tumors that respond durably to a therapy and those that respond only transiently to that therapy. The development of subsequent therapies could vary depending on such a difference. In addition, attention could be directed toward identifying predictors of nonresponse, so that ineffective and toxic therapies could be avoided in patients that lack any chance of responding. The rapid progress in neuroradiological measurement of both morphological and molecular parameters, coupled with the advances in molecular biology of brain tumors that could yield novel surrogate markers through approaches such as expression profiling, have the potential to move neuro-oncology past the "survival-only" mode of translational research (Figure 3).

New Frameworks for Tumor Classification: Rethinking Glioma Cells of Origin

In contrast to the common epithelial human malignancies, the cells of origin for most malignant primary brain tumors remain enigmatic. Their elusive nature has thwarted brain tumor research, in that it has prevented precise comparisons between such normal precursor cells and their neoplastic counterparts. Without knowledge of the originally transformed cells, it is difficult to dissect out tumorigenic events. For instance, the well-studied human colon carcinoma model has enabled the identification of genetic changes that occur in the progression from normal colonic cells to hyperplastic lesions, subsequently to benign tumors, then to frank carcinoma and finally to invasive and metastatic carcinoma. Even in the best-studied glioma model, that of astrocytoma progression, the first step is already a low-grade, invasive malignancy (World Health Organization grade II astrocytoma).

Traditional neuro-oncology has suggested that tumors with an astrocytic phenotype arise from astrocytes or their immediate precursors, oligodendrogliomas from oligodendrocytes or their immediate precursors, and so on. For oncogenic events to occur and undergo selection, however, these cells must be proliferative. Problematically, there is no evidence to suggest that most brain cells are undergoing division normally during adult life. Glial cells could undergo neoplastic events during reactive proliferation, but no epidemiological evidence convincingly links processes likely to evoke reactive

proliferation, such as trauma, with the development of glial brain tumors.[29] Furthermore, for "neuronal" tumors such as medulloblastomas, it is difficult to invoke the mature neuron as a cell of origin, given its terminally differentiated status after fetal life. A clever approach to this problem argued for a window of neoplastic vulnerability, that oncogenic events occurred in still proliferating fetal cells.[30] In this theory, "neuronal" tumors such as medulloblastomas were uncommon and occurred early in life because they underwent oncogenic events during a short period early in embryonic and fetal life, when neuronal cells were still actively dividing. On the other hand, glial tumors were more common and arose later in life, because glial proliferation occurred later, during a longer period in gestational life and in postnatal life as well. Unfortunately, particularly given the impossibility of studying truly premalignant lesions in neuro-oncology (see above), it has not been possible to identify the earliest changes in glioma formation or determine when such changes occur.

Two major scientific advances in the past few years suggest that diffuse gliomas could arise from neuroectodermal stem cells that are present throughout life. The first advance involves research on neuroectodermal stem cells and the second relates to progress in animal modeling. The observation that neuroectodermal stem cells reside in adult human brains[31] raises the logical possibility that this cell population could give rise to gliomas. These stem cells have a proliferative potential, are highly migratory, and can pursue remarkably diverse paths of differentiation—all features intrinsic to glioma cells and likely characteristics for neoplastic cells of origin. The further observation that systemic precursor cells, such as those of the bone marrow,[32] can differentiate along neuroectodermal lines creates the additional possibility that such stem cells could arise or even undergo oncogenic events elsewhere and then proliferate in the apparent immunological safety or nutritive environment of the brain. In this regard, it is of interest that primary central nervous system lymphomas in nonimmunocompromised patients are clonal neoplasms that have undergone germinal center development,[33] and other systemic lymphomas such as intravascular lymphoma preferentially home to brain vasculature. Such findings are consistent with the theory that primary central nervous system lymphomas are systemic tumors that grow preferentially within the central nervous system. Although such a theory would be highly speculative at the present time for primary neuroectodermal tumors, the presence of adult neuroectodermal stem cells provides the first endogenous population that would be likely cells of origin for primary brain tumors.

The ability to manipulate the mouse genome to model human cancer is also now providing remarkable insights into glioma development.[34,35] For studying cells of origin, the most powerful approach to date has involved targeting oncogenic events to specific cell types. By restricting expression of a viral receptor to either progenitor cells or maturing astrocytes, oncogenic stimuli can be directed to these cells.[36] The results of such studies clearly demonstrate a telling histological diversity between tumors arising from progenitor cells undergoing one tumorigenic event and those undergoing another tumorigenic event, as well as between oncogenesis in glial progenitor cells *versus* maturing astrocytes (Figure 4). For instance, overexpressing oncogenic Ras and Akt in progenitor cells, which mimics the elevated activity of these signaling pathways found in human glioblastomas, results in mouse brain tumors that are histologically similar to their human counterparts.[36] Overexpression of platelet-derived growth factor-B in the same cells, however, yields tumors histologically similar to oligodendrogliomas.[37] Nonetheless, it is the similarity that is most striking: these tumors all resemble diffuse gliomas, complete with their characteristic invasive patterns and histological hallmarks of malignancy. These results provide a proof of principle that transformation of glial progenitor cells can result in tumors that have phenotypic properties of astrocytomas or oligodendrogliomas.[38] Interestingly, these lesions do not display overt neuronal properties, perhaps because the experimentally transformed postnatal progenitor cells are restricted to glial differentiation, or because either the brain environment or the intrinsic cellular programs operative in proliferating precursor cells favor glial differentiation. It therefore seems most likely that the activation or inactivation of specific protein pathways must govern the eventual phenotype of subtypes of neoplasms arising from specific precursor cells.

The occurrence of oligoastrocytomas, so-called "mixed gliomas," raises further evidence, both in humans and in the animal models. Oligoastrocytomas are controversial entities, and are variably diagnosed even among experienced neuropathologists.[18] Regardless of diagnostic variations, many diffuse gliomas contain cells with both astrocytic and oligodendroglial morphologies, yet molecular genetic analyses have demonstrated that the phenotypically distinct oligodendroglioma-like and astrocytoma-like regions in oligoastrocytomas have the same genetic alterations.[39] In other words, these are clonal lesions at the genetic level, with remarkable phenotypic diversity. Once again, the mouse models provide intriguing corollary data, because the neoplastic transformation of maturing astrocytes using viral oncogenes can drive these cells toward both oligodendroglial and astrocytic phenotypes in the same tumor, creating genetically engineered murine oligoastrocytomas.[40] On the other hand, diverse oncogenic events, perhaps because of environmental influences, may drive transformed cells toward only a limited number of glial appearances. Dissecting out the roles of "seed" and "soil" will be a major challenge for neuro-oncology throughout the next decade (Louis DN, Posner JB, Jacobs T, Kaplan R: Report of the Brain Tumor Progress Review Group. http://ospncinihgov/prg_assess/prg/btprg/, 2000).

Proposal: Beginning to State the Problem of Glioma Classification in Different Terms

The current histological approach to glioma classification, the product of decades of clinicopathological corre-

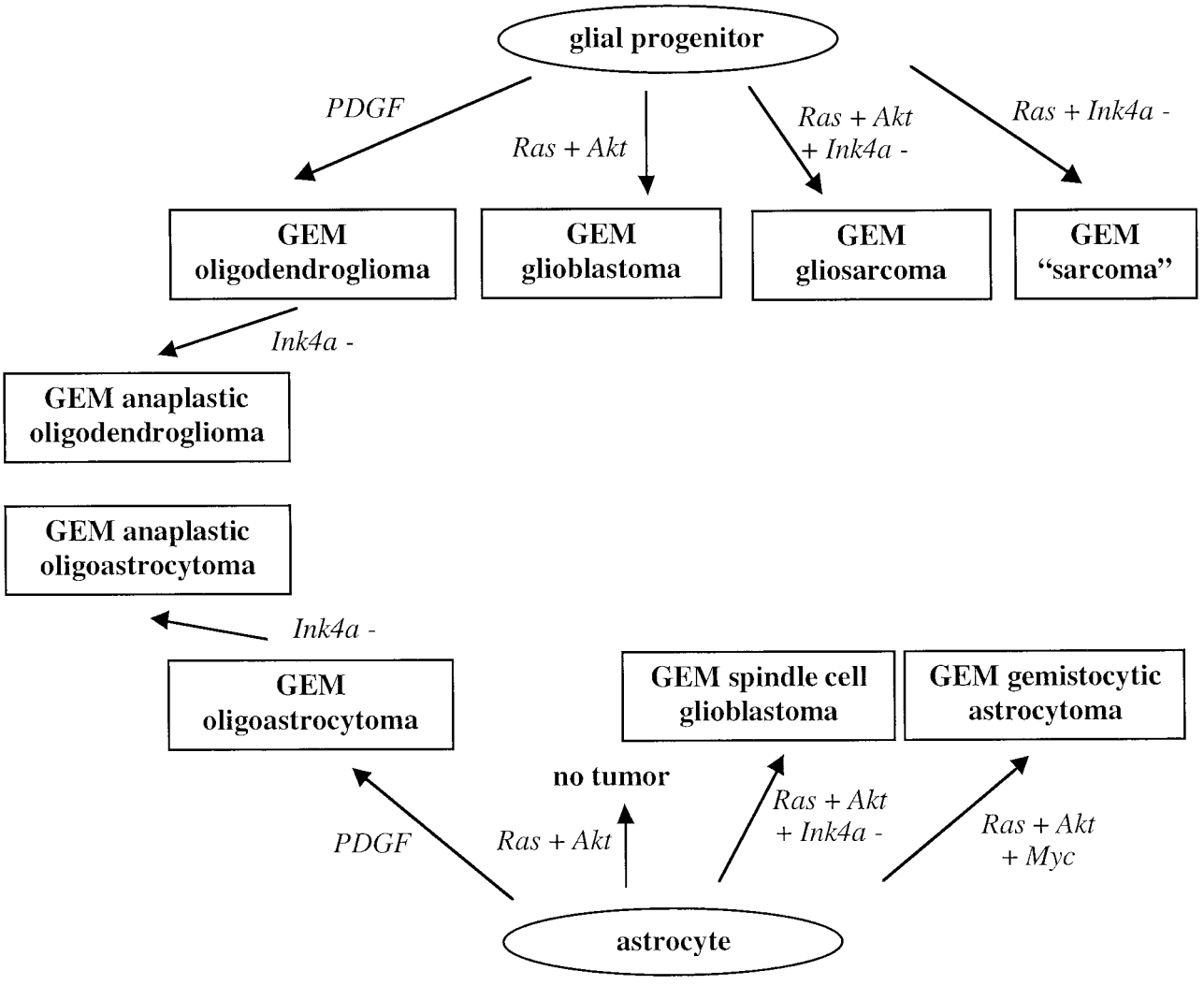

Figure 4. Generation of glioma subtypes in mice. Schematic diagram illustrates signaling pathways, cells of origin, and histological diagnoses of genetically engineered murine (GEM) gliomas. The similarities with human glioma histology and genetics suggest that histological and molecular signaling classification approaches could be related and complementary.

lation, is practical in the majority of situations, and is generally to be praised rather than discarded. But significant advances in molecular genetics, neuroimaging, mouse modeling, and developmental neurobiology encourage a critical reappraisal of glioma classification. The molecular advances have had practical in addition to theoretical ramifications, for instance in the discovery of the prognostic and predictive importance of chromosomal events in oligodendroglial tumors. A reappraisal of glioma classification, therefore, is not simply a hope for the distant future, but a need for the upcoming decade (Louis DN, Posner JB, Jacobs T, Kaplan R: Report of the Brain Tumor Progress Review Group. http://ospncinihgov/prg_assess/prg/btprg/, 2000). To do so, as we have seen in the above discussion, will require progress in three domains: 1) the conceptual framework of classification, 2) the endpoints to measure a classification system, and 3) the techniques used for classification.

Conceptual Framework

The diffuse gliomas that form the bulk of adult neuro-oncology practice are most likely neoplasms that arise from precursor cells or mature cells in which specific genetic alterations lead to a less-differentiated state. These cells are driven to neoplasia by genetic events, the proximate causes of which remain undetermined. The phenotypic end stage is thus a result of the particular genetic events that, possibly in combination with the local environment, alter the activity of particular cellular control pathways. Thus, progenitor cells that undergo *TP53* mutations generally activate pathways that force or permit astrocytic differentiation, whereas similar cells that undergo chromosomal loss of 1p and 19q most often become committed to an oligodendroglial phenotype. Hence the general genetic division of human oligoastrocytomas or oligodendrogliomas into those with either *TP53* mutations or those with 1p and 19q loss, and the

histological correlates of astrocytic and oligodendroglial morphology, respectively. (D. N. Louis and J. G. Cairncross, unpublished data)[23] The phenotypic diversity, however, may be influenced by myriad factors such as the microenvironment, the specific nature of the cell of origin, or the complex interactions of different signaling pathways.

Relevant Endpoints

Clearly the validation of any classification system must remain clinical and practical. A major goal of translational glioma research should therefore be the correlation of clinically useful therapeutic and prognostic endpoints with molecular parameters. Unfortunately, such a goal remains a long way off, given the scarcity of effective therapies, response markers and outcome measures in neuro-oncology; attaining this goal therefore awaits further developments in therapy (Louis DN, Posner JB, Jacobs T, Kaplan R: Report of the Brain Tumor Progress Review Group. http://ospncinihgov/prg_assess/prg/btprg/, 2000). Nonetheless, it remains possible that novel therapies will prove effective for specific molecular variants of malignant glioma, as in the case of PCV chemotherapy in those anaplastic oligodendrogliomas that lose 1p and 19q. For this reason, it is essential that new trials incorporate molecular measurements to assess whether responses are occurring in molecular subsets. At the present time, we suggest that glioblastoma and anaplastic astrocytoma trials include analyses for *TP53* mutation *versus EGFR* amplification, because these two variables are so dichotomous and correlate with significant clinicopathological variables such as age and previous low-grade tumor. For all malignant glioma trials, including those studying glioblastoma, anaplastic astrocytoma, oligodendroglioma, and anaplastic oligodendrogliomas, analysis of 1p and 19q status is clearly essential—to subdivide the oligodendroglial tumors and to cull out oligodendroglial-like tumors included in high-grade astrocytoma trials. In the future, clinical trials may even use molecular classification to stratify patients into treatment arms.

Techniques of Classification

History suggests that molecular profiling will not replace histology entirely, or at least not in the near future. Ultrastructural and immunohistochemical analyses provided valuable ancillary techniques for tumor classification, but did not supplant standard light microscopic evaluation. Histological examination is simple and efficient and, as a result, should be part of the diagnostic armamentarium for many years to come. Nonetheless, molecular approaches—such as mRNA expression profiling and eventually delineation of protein pathway activity —will no doubt refine tumor classification. Novel methods may also come from other disciplines, such as neuroradiology. Neuroimaging is rapidly improving in its ability to anatomically define tumors, and could eventually provide highly detailed phenotypic pictures of tumors within the brain. Furthermore, neuroimaging of molecular parameters is a reality as well, with techniques such as magnetic resonance spectroscopy able to derive metabolic information on tumors without tissue sampling. These developments suggest that neuroradiological approaches could eventually image biochemical effects of specific gene alterations. As such techniques improve, both in morphological resolution and in molecular measurements, tumor classification may fall under the provenance of neuroradiologists in addition to neuropathologists.

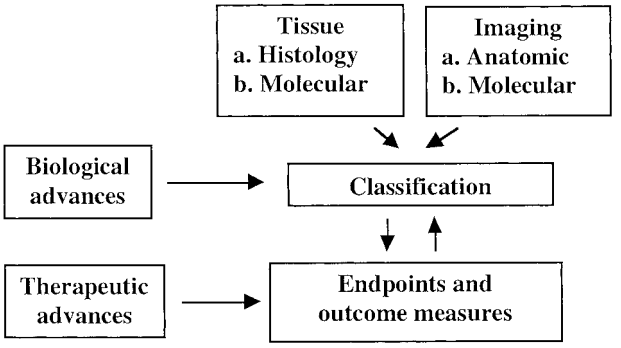

Figure 5. Future classifications. These will be based on input from traditional as well as molecular analyses, and will involve both tissue-based and imaging modalities. The classification will have to incorporate new frameworks based on biological advances. Most significantly, the classification will have to correlate closely with clinically relevant endpoints and, as new outcome measures and effective therapies are developed, will have to modified by such correlations.

The hope for the future is a classification system, based on both phenotypic and molecular features, that provides accurate prediction of response to effective therapies and lack of response to ineffective, toxic therapies (Figure 5). In a sense, the long-term goal will be to mimic the development throughout the past century in the treatment of infectious diseases. With the precise classification of different kinds of bacteria and the advent of numerous antibiotics, one can intelligently direct specific antibiotics to treat distinct bacterial infections. A molecular classification system for gliomas will similarly shift drug development paradigms toward more diverse therapies based on correcting specific cellular defects, and away from the unidimensional toxic strategies that have dominated neuro-oncology for the past half century. For the first time, the beginnings of such a system can be imagined.

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