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Meeting Report

Mouse Models of Human Cancer Consortium Symposium on Nervous System Tumors[1]

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Abstract

Nervous system tumors represent unique neoplasms that arise within the central and peripheral nervous system. Recent progress in generating genetically engineered mouse models of these tumors has advanced our understanding of the critical molecular and cellular events important for the development of these tumors. Recently, the National Cancer Institute-sponsored Mouse Models of Human Cancer Consortium convened a meeting on Nervous System Tumors to review recent advances and suggest directions for future research. Refined and novel approaches to modeling central nervous system tumors, including gliomas, meningiomas, medulloblastomas, and oligodendrogliomas, as well as peripheral nervous system tumors such as neurofibromas, schwannomas, and malignant peripheral nerve sheath tumors, were presented. In this review, we discuss the current status of mouse modeling of human nervous system cancers with a specific focus on unresolved scientific questions pertaining to the molecular genetics and cellular biology of these tumors.

Introduction

Nervous system tumors represent a unique challenge to clinicians because of the complexity of the brain, the difficulty in identifying precancerous lesions, and the limited effective therapies available (1). These tumors include those that grow within the CNS[3] (glioma, medulloblastoma, ependymoma, and meningioma), as well as those that are associated with peripheral nerves (schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor). Unlike other organ sites, screening of presymptomatic individuals is not possible, and tumors often grow to a considerable size before detection. In addition, there are very few successful therapeutic options, besides surgery, that have demonstrated effective local control and none, in the case of high-grade gliomas, that alter the long-term clinical outcome. The development and evaluation of effective therapies would be accelerated by the generation of adequate small animal tumor models that accurately recapitulate their human counterparts. The purpose of this meeting summary was to provide a current update of progress in the development, refinement, and application of mouse modeling of nervous system tumors, as well as to outline future directions for scientific investigation.

Initial models of human nervous system tumors focused on the use of established tumor cell lines with specific genetic changes or human tumor explants grown in rodents (2), but over the past several years, the focus has shifted to the generation of mice with specific genetic changes that represent the common genetic alterations seen in human tumors (3). This approach has led to the development of GEM for each of the major nervous system tumor types. Within the CNS, four major tumor types have been successfully modeled, including astrocytoma (glioma), oligodendroglioma, medulloblastoma, and meningioma (4). In the PNS, Schwann cell tumors (schwannomas, neurofibromas, and MPNSTs) have also been accurately modeled in GEM.

Common Themes. On the basis of molecular genetic analyses of human tumors, there are genetic changes that occur commonly in the benign, low-grade tumors (initiating genetic changes), and other genetic alterations identified almost exclusively in high-grade tumors (progression-associated, cooperating genetic changes). Some of the specific initiating genetic events chosen for mouse modeling were based on the genes mutated in inherited cancer syndromes where affected individuals are prone to the development of nervous system tumors (5). In recent years, mouse models that use conventional gene targeting (standard knockout mice), conditional tissue-specific knockout mice, and viral-mediated transgene delivery have been developed. Each of these approaches has its strengths and limitations, but all have proven that robust, accurate, small animal models of human nervous system tumors can be generated. Significant progress in adapting these models for preclinical applications has been made. Small animal imaging, including MRI, computerized tomography, and PET, have been used to detect many of these tumors in the living animal and follow their growth longitudinally.

With the development of these mouse models, it has become possible to exploit GEM to address basic questions in cancer biology. In the case of many CNS tumors, the precise cell of origin is unknown. Although it is presumed that gliomas arise from astroglial cells and meningiomas arise from leptomeningeal cells, it is becoming increasingly clear that the consequences of specific genetic alterations have different effects depending on the developmental state of the cell (6). A common theme discussed in this meeting concerned the use of GEM to elucidate the cell of origin for CNS tumors.

A second theme important in cancer progression involved the identification and characterization of cooperating, progression-associated, genetic changes. A number of specific genes have been studied and found to accelerate tumor development or promote malignant progression. These cooperating genetic events represent alterations in growth factor receptors or cell cycle regulatory genes. In addition to known cooperating genetic events, mouse models are now used to identify novel progression-associated events that may represent additional targets for therapeutic drug design and tumor monitoring.

In addition to specific genetic events that promote tumorigenesis, there are undoubtedly modifying genes in each of our genetic make-up that attenuate the probability that we will develop cancer. It

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[3] The abbreviations used are: CNS, central nervous system; GEM, genetically engineered mice; PNS, peripheral nervous system; MPNST, malignant peripheral nerve sheath tumor; EGFR, epidermal growth factor receptor; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; PET, positron emission tomography; RB, retinoblastoma; Hif-1α, hypoxia-inducible factor 1α; PDGF, platelet-derived growth factor; Shh, Sonic Hedgehog; Nf, neurofibromatosis; RCAS, replication-competent, ALV-LTR, splice acceptor; TOR, target of rapamycin.

is not known how many of such genes exist or how best to identify them in humans. However, GEM modeling using inbred strains with defined genetic backgrounds offers the opportunity to find these genes in mice. Mice with differing susceptibilities to nervous system tumors have been identified, and strategies have been developed to locate the modifiers that account for these differences.

Astrocytoma. Robert Bachoo *et al.* (Ref. 7; Dana-Farber Cancer Institute) developed a mouse glioma model by infecting astrocytes *in vitro* with a retrovirus expressing an activated allele of the EGFR. They demonstrated that EGFR-expressing *Ink4a/Arf*$^{-/-}$, but not *Ink4a*$^{-/-}$ or *Arf*$^{-/-}$, astrocytes formed neurospheres, which when injected into the brains of naive animals, resulted in the formation of infiltrating high-grade astrocytomas. They also presented early data tracking the malignant progression of these tumors using both genomic and expression array based techniques. To model RB pathway mutations in infiltrating gliomas, Terry Van Dyke (University of North Carolina) presented work using a fragment of the SV40 T antigen (T_{121}), which binds RB as well as the RB family members p107 and p130. Expression of a conditional allele of T_{121} under control of the astrocyte-specific GFAP promoter led to astrocytoma formation in conditionally transgenic mice. Tumors showed increased proliferation and areas of apoptosis but no microvascular proliferation. Tumors latency was additionally shortened by the introduction of a mutant *Pten* allele (8).

Ab Guha *et al.* (University of Toronto) presented a model of high-grade astrocytoma in which oncogenic RAS was expressed in astrocytes of transgenic mice *in vivo*. These B8 RAS transgenic mice develop astrocytomas by 3–4 months of age with histopathological features of their human counterparts. To model astrocytoma progression, they developed an additional transgenic strain that expresses the activated EGFRvIII mutation in astrocytes. EGFRvIII transgenic mice do not develop astrocytomas, even after 18–20 months of age, however, mice expressing both activated RAS and the EGFRvIII mutation die within 2 months of more aggressive glial neoplasms (9). Histopathological and immunochemical characterization of these tumors demonstrated that these tumors were oligodendrogliomas or mixed oligoastrocytomas, suggesting that the cooperative effect of constitutive EGFR signaling alters the histological features and biological characteristics of RAS-induced astrocytomas.

David Gutmann *et al.* (Ref. 10; Washington University) developed mice with astrocyte-specific Cre recombinase expression as a genetic tool for inactivating astrocytoma-associated genes in astrocytes in conditional knockout mice *in vivo*. They presented their studies on inactivation of the *Nf1* and *tuberous sclerosis complex 1* genes in astrocytes and demonstrated that mice lacking these tumor suppressor genes in astrocytes exhibit specific astrocyte growth defects. In addition, they used Affymetrix-based gene expression profiling of RAS-transgenic mouse gliomas (in collaboration with Dr. Guha) to identify additional astrocytoma-associated genes (11). Several of the transcripts identified were implicated in both rodent and human glioma formation. More detailed analyses of two of these glioma-associated genes, GAP43 and T-cadherin, revealed unanticipated mechanisms of action. These studies underscore the power of mouse models to identify novel genes in tumorigenesis that might serve as future therapeutic targets.

Karlyne Reilly *et al.* (National Cancer Institute) presented an astrocytoma model in mice doubly heterozygous for targeted mutations in *Nf1* and *p53*. Mice in which both mutant alleles were on the same chromosome (*Nf1;p53 cis* mice) were predisposed to high-grade glioblastoma multiforme astrocytomas through loss of the wild type *Nf1* and *p53* alleles (12). In addition, tumor grade and penetrance were increased in mice maintained on the C57BL/6 inbred genetic background in contrast to mice maintained on the 129sv genetic background. Current studies are focused on identifying glioma susceptibility modifier genes.

Recent studies have implicated both microvascular proliferation and hypoxia in astrocytoma progression. Hypoxia is thought to be a factor in the control of angiogenesis, cell cycle progression, and cell survival through up-regulation of the Hif-1α transcription factor. To address the role of Hif-1α in astrocytoma formation in mice, Gabriele Bergers (University of California-San Francisco) in collaboration with Randall Johnson (University of California-Santa Cruz) generated Hif1$\alpha^{-/-}$ astrocytomas that were incapable of responding to hypoxia. In s.c. xenografts, loss of Hif-1α led to the formation of smaller tumors than expected, however, intracranial xenografts of transformed Hif-1$\alpha^{-/-}$ astrocytes were highly invasive and exhibited increased tumor growth, decreased necrosis, and increased vascularity. These data raise questions as to whether inhibition of Hif1α will be beneficial for the treatment of patients with infiltrating glioma.

Oligodendroglioma. Eric Holland (Memorial Sloan Kettering Cancer Center) presented an update on the use of avian retroviral vectors (RCAS) to selectively infect glial or glial progenitor cells in mice transgenic for the avian retrovirus receptor (Tv-a) under control of the nestin or GFAP promoters. Infection of mice with viruses containing activated RAS and activated AKT led to astrocytoma formation, whereas infection of *nestin*-Tv-a mice with RCAS virus expressing PDGF-B led to oligodendroglioma development. Ongoing experiments include treatment of these models with therapies targeted against the initiating events or against angiogenesis and monitoring with MRI (13).

William Weiss *et al.* (University of California-San Francisco) directed expression of an activated *EGFR* allele using the S100β promoter to generate mice that develop low-grade oligodendroglioma. S100β*–v-erbB* transgenic mice, also deleted for *Ink4a/Arf*, developed tumors with shortened latency, increased grade, and increased penetrance. In collaboration with Kevan Shokat (University of California-San Francisco), the ATP binding domain of *v-erbB* was mutagenized to retain transforming potential but could be selectively inhibited with the drug Naphthyl PP1. Using the tetracycline-regulatable system, they generated transgenic mice that coexpress the Naphthyl PP1-sensitive v-*erbB* allele along with a luciferase reporter gene. Preliminary data demonstrated that the resulting mice developed glioma that could be monitored in the live animal using luciferase-based bioluminescence imaging.

Bengt Westermark *et al.* (Uppsala Universitet) transduced PDGF-B using murine leukemia viruses intracranially into mice and observed both astrocytoma and oligodendroglioma formation. They hypothesized that these tumors were formed through autocrine stimulation of the PDGF pathway in combination with additional genetic alterations created by the insertion of the retrovirus (*e.g.*, activation of oncogenes by enhancer insertion or deletion of tumor suppressors by direct viral integration into coding or regulatory sequences). They used an inverse PCR-based strategy to identify potential tumorgenic insertion sites and found >20 integration sites, including regions corresponding to oncogenes and tumor suppressors known to play a role in human glioma development, as well as additional loci that map to regions orthologous to those implicated in human tumors.

Medulloblastoma. Mutations in the human homologue of patched (*PTCH*) occur in a subset of hereditary and sporadic medulloblastoma. To evaluate this gene in a mouse model, *Ptc1*$^{+/-}$ mice were generated in Matthew Scott's laboratory and found to have a 14% incidence of medulloblastoma, which is additionally increased to 100% in combination with *p53* deletion (14). Ryan Corcoran (Stanford University) presented their current strategy to identify relevant targets of the Ptc1 signaling pathway by finding common tumor-specific expression patterns using gene expression profiling.

A new model for medulloblastoma was developed by overexpression of Myc and Shh, a key signaling molecule in the Ptc1 pathway. The RCAS-TVA system was exploited to introduce retroviruses expressing Myc and Shh into *nestin-tva* transgenic mice. Daniel Fults (University of Utah) previously reported that ectopic expression of Myc in neural progenitors in the cerebellum resulted in cell aggregates within the leptomeninges but not tumor formation (15). At the meeting, he showed that overexpression of *Shh*, a potent mitogen for cerebellar granule cell precursors, induced medulloblastoma in 9% of mice, whereas the introduction of *Shh* in combination with Myc had a synergistic effect, increasing tumor incidence to 23% (D. Fults, unpublished results).

Several knockout mouse models generated to address fundamental questions of cell cycle regulation and genotoxic stress unexpectedly resulted in new models of medulloblastoma. During a series of knockout experiments designed to evaluate the effects of combined loss of multiple cell cycle regulatory genes, Martine Roussel (St. Jude Children's Research Hospital) discovered that disruption of *p53* in conjunction with inactivation of cyclin-dependent kinase regulatory genes (*Ink4c*, *Ink4d*, or *Kip1*) resulted in medulloblastoma with a 3–10% incidence (M. Roussel, unpublished results). Deletion of *DNA Ligase 4* (*Lig4*) induces genotoxic stress and results in widespread neural apoptosis and embryonic lethality. Peter McKinnon *et al.* (St. Jude Children's Research Hospital) bred *Lig4*-deficient mice with $p53^{-/-}$ mice to rescue the apoptosis caused by genotoxic stress. Although deletion of p53 blocked the widespread apoptosis and prevented embryonic lethality in $Lig4^{-/-}$ mice, unexpectedly, 100% of $Lig4^{-/-};p53^{-/-}$ mice developed medulloblastoma (16).

All of the medulloblastoma models presented were histologically similar to their human counterpart. To evaluate the molecular similarities in mouse medulloblastoma models generated by the introduction of mutations in different genetic pathways, Peter McKinnon compared gene expression profiles from a number of mouse medulloblastoma models, including $Lig4^{-/-};p53^{-/-}$ mice, several different combinations of cell cycle regulatory pathway mouse mutants from Martine Roussel, as well as $Ptc1^{+/-}$ and $Ptc1^{+/-};p53^{-/-}$ mice from Tom Curran (St. Jude Children's Research Hospital). All medulloblastomas exhibited gene expression profiles that were more similar to developing cerebellum than to adult cerebellum, supporting the prevailing hypothesis that medulloblastomas arise from cerebellar granule cell precursors in the external germinal layer during development. Surprisingly, the gene expression profiles from tumors arising from mutations in different genetic pathways shared a number of common gene expression patterns that were distinct from normal developing and adult cerebellum and were presumed to be tumor specific (P. McKinnon, unpublished results).

The presentation of two models with conditional inactivation of *Pten* in the cerebellum highlighted the use of Cre-lox technology to reveal multiple roles for a gene by studying function at different stages of development. Silvia Marino *et al.* (University Hospital, Zurich, Switzerland) bred *engrailed 2-cre*-transgenic mice with *Pten-loxP* mice to induce *Pten* deletion at embryonic day 9.5 in a brain region that later gives rise to the medial region of the cerebellum (17). Suzanne Baker *et al.* (St. Jude Children's Research Hospital) generated a *Gfap-Cre*-transgenic mouse that induced *Pten* deletion in cerebellar granule neurons and dentate gyrus granule neurons around postnatal day 14 (18). Deletion of *Pten* during embryonic development revealed a critical role in cell migration and appropriate patterning in the cerebellum, whereas postnatal deletion revealed a requirement for *Pten* in cell-autonomous control of neuronal size in adulthood. Despite the established role for Pten in cell cycle regulation in a number of experimental paradigms, *Pten* deletion did not cause ongoing proliferation in neurons in either model. Because TOR functions downstream of PTEN in *Drosophila*, Baker *et al.* tested the effects of the mammalian TOR (mTOR) inhibitor CCI-779 on the phenotype of *Pten* conditional knockout mice and found that CCI-779 prevented the increase in soma size in young mice, and reversed neuronal enlargement in adult mice. These results indicate that mTOR is a major effector of neuronal growth regulation downstream of Pten, and suggest a therapeutic potential for mTOR inhibitors in treating pathological conditions in the brain resulting from *PTEN* deficiency (S. Baker, unpublished results).

Meningioma. Mouse models of meningioma have been challenging because of the lack of leptomeningeal-specific Cre-transgenic mice. To circumvent this problem, Marco Giovannini *et al.* (INSERM, France) combined adenoviral Cre delivery with conditional knockout strategies. Mice expressing conditional $Nf2^{flox}$ alleles were injected with adenoviral-expressing Cre into the cerebrospinal space to achieve leptomeningeal *Nf2* inactivation. The *Nf2* gene was chosen for inactivation based on the observations that individuals with the NF2-inherited cancer syndrome develop meningiomas and that *NF2* gene inactivation is found in >50% of sporadic human meningiomas. Leptomeningeal *Nf2* inactivation resulted in leptomeningeal hyperplasia and meningioma formation (19). In addition, hemizygosity for *p53* had no effect on meningioma formation or progression. Studies are in progress to determine the contribution of *p16* inactivation to meningioma development and progression in this mouse model.

PNS Tumors. Tumors of the PNS include neurofibromas, schwannomas, and MPNSTs. All of these tumor types involve neoplastic Schwann cells. Individuals affected with the inherited cancer syndromes, NF1 and NF2, are prone to the development of neurofibromas and MPNSTs (NF1) as well as schwannomas (NF2). Because mice heterozygous for a targeted mutation in either the *Nf1* (neurofibromin) or *Nf2* (merlin or schwannomin) gene do not develop these tumors, recent work has focused on generating tissue-specific conditional knockout mice and studying the contribution of cooperating genetic events on MPNST development.

Neurofibromas in mice have been modeled by injecting varying numbers of $Nf1^{-/-}$ embryonic stem cells into blastocyst-stage embryos (5), as well as by using transgenic Krox20-Cre mice to inactivate *Nf1* in Schwann cells (20). In humans, the progression from benign neurofibroma to MPNST involves additional cooperating changes, including *p53* and *p16* gene inactivation. In support of this genetic cooperativity, mice heterozygous for both *Nf1* and *p53* mutations ($Nf1^{+/-};p53^{+/-}$, *cis* mice) develop high-grade MPNSTs, histopathologically similar to their human counterparts (5). Jennifer Gordon *et al.* (Temple University) described their preliminary finding that a small subset of mice expressing the human JC polyoma virus T antigen under the control of the Mad4 promoter develops high-grade soft tissue tumors histologically similar to MPNSTs. Ongoing studies are focused on understanding the interaction between JC polyoma virus T-antigen expression and *NF* gene function.

Marco Giovannini *et al.* have successfully generated mouse models of schwannoma by inactivating *Nf2* in Schwann cells using the Schwann cell-specific P0 promoter. Schwann cell hyperplasia and schwannomas were produced either by expressing a dominant inhibitory *Nf2* allele in Schwann cells or by biallelic *Nf2* inactivation using Cre/Lox technology (5). Andrea McClatchey *et al.* (Massachusetts General Hospital) described their studies on the function of the *Nf2* gene product, merlin, in the regulation of Schwann cell growth. They report that mice heterozygous for targeted mutations in both the *Nf1* and *Nf2* genes are prone to the development of MPNSTs, suggesting that combined merlin and neurofibromin dysfunction contributes to malignant Schwann cell tumor formation.

Small-Animal Neuroimaging. The introduction of new small-animal imaging technologies has accelerated recent advances in mouse cancer modeling. The two human imaging modalities that have been adapted for mouse tumor studies, MRI and PET, were discussed by Joel Garbow (Washington University).

MRI is a powerful and versatile imaging modality for animal tumor studies that provides excellent soft tissue contrast and outstanding anatomical resolution by taking advantage of the ability of MRI to detect specific biophysical magnetic signatures of tissues. MRI has been used to longitudinally monitor tumor growth and response to therapy (21), as well as to measure edema, changes in white matter fibers resulting from tumor growth, breakdown of the blood-brain barrier, and changes in vascular density, blood flow, and permeability resulting from angiogenesis. Progress in small-animal imaging has been accelerated by the development of dedicated small-animal imaging systems with increased magnetic field strengths not yet available for human clinical studies. In addition, the availability of gadolinium-based (T1 agent) contrast agent for visualizing tumors and iron particle labeling of microglia (T2 agent) in rodent glioma models has improved the contrast sensitivity for tumor detection by MRI.

A great strength of PET lies in its unique ability to map biochemistry and biological function, thereby providing physiological information about tumors. Using radiolabeled tracers, PET is widely used in humans to monitor cancer progression and response to therapy. Its use in animals has increased with the recent development of PET systems optimized for and dedicated to the study of rodents. Radiolabeled tracers (*e.g.,* ^{18}fluoro-deoxyglucose, ^{18}fluoro-thymidine) have been used to measure tumor metabolism and proliferation, whereas a wide variety of radiopharmaceuticals have been developed for targeting specific receptors within the brain.

Darlene Jenkins (Xenogen Corporation) discussed optical techniques as an additional noninvasive imaging modality useful for studying brain tumors. The use of luciferase reporter systems for bioluminescence tumor monitoring in animals *in vivo* is now easily accomplished using a charge coupled device-based, low-light imaging system (22).

Summary and Future Directions. This mouse models of human cancer consortium symposium on nervous system tumors highlighted the excellent progress made to develop robust preclinical models for both CNS and PNS tumors. Multiple complementary approaches were used for these studies, each of which could be melded with another approach to answer specific questions regarding cooperating genetic events and host-brain environment. For example, conditional knockout mice are now being used in combination with RCAS/TVA methodology to inactivate specific genes (using Cre recombinase) in combination with overexpression of additional cooperating genes. Similarly, conditional knockout or transgenic mice bearing abnormalities in vascular endothelial growth factor receptor expression are being utilized for traditional tumor cell line explant studies to evaluate the role of the brain vascular response to tumor formation and progression.

We are now entering into a second phase of mouse modeling that requires an emphasis on *trans*-disciplinary approaches to the design, analysis, and applications of mouse cancer models. In addition, there are a number of key questions that mouse modeling may be able to answer that cannot be addressed by analyzing human tumors. With robust and accurate mouse models of nervous system tumors, we have the ability to collect information on the earliest neoplastic changes associated with tumorigenesis, determine the impact of the host-brain/peripheral nerve microenvironment on tumor initiation and progression, and define the anatomical and histopathological correlates for the radiographic changes on conventional imaging studies. As we begin to unravel some of these mysteries, our abilities to design targeted therapies and devise more optimized management strategies for human nervous system tumors will undoubtedly improve.

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