Polyomavirus and Medulloblastoma: A Smoking Gun or Guilt By Association?

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Brain tumors are an important cause of cancer morbidity and mortality, particularly in children, where it will soon surpass leukemia as the leading cause of pediatric cancer-related deaths in the United States. Although the actual incidence of primary brain tumors is relatively low compared with the more common epithelial tumors, their significant contribution to the overall cancer mortality in this country is a testament to their lethality. Therapeutic advances for primary brain tumors have come painstakingly slowly as a result of both their intrinsic resistance to standard cytotoxic therapies as well as their anatomical location within the exquisitely sensitive tissue of the central nervous system (CNS), limiting the extent to which surgical resection and radiation therapy can be safely accomplished. Medulloblastomas, the most common malignant brain tumors in children, are embryonal tumors (formally described as primitive neuroectodermal tumors, or PNETs) of the cerebellum and account for approximately 20% of all childhood brain tumors. These tumors are thought to arise from either the neural stem cells of the subependymal zone of the fourth ventricle or from the granule cell progenitors (GCPs) destined to form the external granule layer of the cerebellum, where they will ultimately form the granule cells that help regulate the activity of cerebellar purkinje cells. These tumors are highly aggressive and, in contrast to the more common gliomas, have a high propensity for spreading along cerebral spinal fluid pathways and metastasizing widely both within the CNS and systemically. Although many patients who develop medulloblastoma can be cured of their disease with aggressive surgery, cranial spinal radiation, and chemotherapy, nearly half of all children afflicted with this tumor still die of their disease. Furthermore, subgroups of patients, such as the very young (<2 years of age) and those who present with metastatic disease, have particularly poor prognoses. Finally, many of the children who are cured of their tumors by aggressive multimodality therapy are left with lifelong physical and neurocognitive deficits.

Understanding the molecular pathogenesis of a disease offers an opportunity for identifying novel signal transduction pathways, resulting in the discovery of novel therapeutic targets. Better yet, if the pathogenic mechanism(s) of an illness can be shown to be an environmental insult (i.e., infection), one can envision potential preventative approaches to the disease. Thus, the study by Del Valle et al. (1) in this issue should be of interest for those interested in neuro-oncology as well as those interested in cancer pathogenesis. Del Valle et al. demonstrate the presence of JC virus (JCV) T antigen (Tag), and agnoprotein DNA in 65% and 69% of 20 and 16 medulloblastoma specimens, respectively. They further demonstrate the presence of agnoprotein and Tag in approximately half of these tumor specimens, although not always within the same tumor. The authors conclude that the finding of agnoprotein expression in the absence of Tag expression in some tumors suggests a role for agnoprotein (a protein with no currently known function) in pathways involved in the development of JCV-associated medulloblastoma. Though certainly a provocative assertion, one must first step back and ask the more general question of whether JCV plays any role at all in the pathogenesis of medulloblastoma. For although a growing number of reports confirm the existence of JCV genomic DNA in a subpopulation of medulloblastomas, the presence of these sequences in tumor cells may merely represent genetic remnants of a prior abortive infection in an earlier progenitor cell that ultimately happened to turn tumorigenic. Thus, to address the question of the causative role of JCV in medulloblastoma, one must critically evaluate the current body of data regarding the genetic mechanisms by which JCV transform cells in vitro and in vivo and compare those mechanisms to those shown to be operative in the pathogenesis of medulloblastomas.

It has been known for years that inoculation of replication-competent JCV into the brains of monkeys leads to the induction of brain tumors in nearly 100% of animals after a 12–24-month latency period (2). Nevertheless, the tumors produced are exclusively glial, rather than embryonal, in origin. Furthermore, JCV does not induce brain tumors of any kind in nonhuman primates other than the new world, owl, and squirrel monkeys. So how might JCV induce medulloblastomas? Not withstanding the results of Del Valle et al. regarding the presence of the agnoprotein in tumor cells, Tag still remains the most likely culprit. Both Tag and the early portion of the JCV genome (which contains the Tag gene) can induce tumors in transgenic animals with histologic features similar to medulloblastoma, particularly when driven by a promoter that is active in primitive neuroectodermal cells. One must be cautious, however, in overinterpreting such observations, as Tag is a powerful oncogene that has been used to induce many different tumor types in various tissue-selective transgenic models. Recent non-Tag-gene-containing mouse models of medulloblastoma, however, have lent some additional crediblility to the argument that Tag could be in part responsible for the induction of a subset of human medulloblastoma. The transforming ability of Tag is at a minimum related to its ability to bind and functionally deregulate the protein products of two prototypic tumor suppressor genes, retinoblastoma (Rb) and p53 (also known as TP53). This may be pertinent given the recent demonstration by Marino et al. (3) that 100% of conditionally rb-null/p53-null transgenic mice develop cerebellar tumors that are histologically identical to medulloblastomas. More evidence in mice suggesting a role for p53 inactivation in the pathogenesis of medulloblastoma-like tumors come from Wetmore et al. (4), who observed an increased incidence of tumor formation from

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rate from the p53 locus (9). Thus, the different pathways that have been variously ascribed to the pathogenesis of medulloblastomas (i.e., p53, APC/β-catenin, Shh, and Tag) may only be responsible for expansion of a population of potential normal target cells (i.e., GCP). These target cells are then susceptible to the eventual genetic hit(s) (i.e., loss of the putative tumor suppressor in 17p13.3) that mediate the transforming events ultimately responsible for the malignant phenotype. New high-throughput genomic and proteomic analyses, such as microarray gene expression profiling, should begin to differentiate between these two possibilities (10). For example, a highly specific gene expression profile(s) and/or proteomic profile(s) should be found in most medulloblastomas if they are the result of a common transforming event, compared with the diverse patterns that would be expected should these tumors be the result of various different genetic aberrations. If the latter is true and JCV is partially or wholly responsible for the malignant phenotype, then expression profiling and other molecular characterization should be able to distinguish tumors harboring and expressing JCV genomes as a distinct subgroup of medulloblastomas. Alternatively, if JCV’s role is limited to the expansion of a target cell population susceptible to later genetic hits, it may never be possible to conclusively determine the contribution of JCV to the development of medulloblastomas through these genetic analyses. Then, only possibly through well-controlled epidemiological case–control studies evaluating large numbers of both normal and tumor-associated brains for the presence of JCV, will we have a chance of determining the relative contribution of the virus toward tumor promotion.

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10% to 100% in animals heterozygous for the patched gene when crossed to a p53-null background. Finally, patients with Li–Fraumeni syndrome, a syndrome characterized by germline mutations of p53, are at an increased risk of developing medulloblastomas (although curiously, p53-null animals do not get medulloblastomas) (4).

So, is it fair to say that Tag plays a role in the induction of medulloblastoma through its effects on p53 and possibly Rb? Maybe; however, there is one problem with this argument. Mutations in p53 (other than in patients with Li–Fraumeni syndrome), Rb deletions, and/or deregulation of Rb through the loss of p16, or Cyclin D1 or CDK4 overexpression are rarely, if ever, found in sporadic human medulloblastomas. What, then, are the pathways known to be deregulated in human medulloblastomas? None uniformly, although there are at least two that have been identified both in specific familial tumor syndromes and in some sporadic tumors. Sonic hedgehog (Shh) is a secreted protein vital for developmental patterning of the CNS, skin, limbs, and other organs (5,6). Shh interacts with a transmembrane receptor, PATCH, to relieve the repression on a series of transcription factors of the gli family, allowing proliferation of GCPs. Patients with Gorlin Syndrome have germline mutations in patched gene and have nearly a 20 000-fold increased rate of medulloblastoma compared with the normal population. Mutations in this signal transduction pathway have also been found in a subset of sporadic medulloblastomas. The other pathway of apparent importance in the development of human medulloblastoma is the Wnt pathway. Wnt is another secreted protein important for developmental patterning, cell growth, and fate determination (7). Wnt signals through the frizzled receptor, inhibiting the glycosyl synthase kinase 3β (GSK3β)/APC (adenomatous polyposis coli gene)-containing complex, thereby preventing the destructive effects on β-catenin. This allows β-catenin to accumulate and translocate to the nucleus, where it activates the LEF (lymphoid enhancer factor)-1/TCF (T-cell factor) family of transcription factors that regulate genes important in cell cycle control including c-myc and cyclin D1. Patients with Turcot syndrome characterized by APC mutations are not only at risk for colon polyps and carcinoma but also for gliomas and medulloblastomas (>90-fold increased risk). Sporadic APC and β-catenin mutations have also been seen (albeit infrequently) in sporadic medulloblastoma. Although there is a recent report suggesting a possible association between Tag and β-catenin (8), there are no firm data suggesting that JCV interacts with either the Shh or Wnt pathways.

So where does this confusing and at times contradictory panoply of observations leave us relative to the molecular pathogenesis of human medulloblastoma and the possible contributing role of JCV? The current data demonstrating the diversity of genetic abnormalities without any one common abnormality suggest that human medulloblastomas may be a heterogeneous tumor “syndrome” resulting from different mutational events in a common precursor (i.e., GCP or neural stem cells). Alternately, it may still turn out that most medulloblastomas are derived from a common set of genetic/epigenetic aberrations that have yet to be identified. For instance, it has been reported that 30%–50% of medulloblastomas appear to have deletions or rearrangements in chromosome 17p, in a region (17p13.3) se-