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A Malignant Oligarchy: Progenitors Govern the Behavior of Oligodendrogliomas

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Recent studies have suggested that brain tumors arise from neural stem cells and are maintained by stem-like tumor-initiating cells (TICs). In this issue of *Cancer Cell*, Persson et al. report that oligodendrogliomas, unlike malignant astrocytomas, originate from—and are propagated by—cells that resemble oligodendrocyte progenitors.

Before the advent of Google and Facebook, if you wanted to know something about a stranger, you'd ask where they were born, who their parents were, and what they did for a living. Just as you can tell a lot about a person's character by knowing where they come from, you can learn a lot about a cancer by understanding its origins. Identifying the cell from which a tumor arises allows investigators to define key similarities and differences between tumor cells and their normal counterparts that may facilitate tumor cell targeting. In addition, cells resembling the cell of origin may persist in tumors and may be essential for long-term tumor growth. If so, identifying the cell of origin, and understanding its vulnerabilities, may be critical for developing more effective therapies.

Gliomas—including astrocytomas and oligodendrogliomas—are the most common primary brain tumors in adults. Despite extensive research into the molecular basis of gliomas, current therapies remain ineffective, and the majority of patients die from their disease. More effective therapeutic strategies are likely to come from a deeper understanding of glioma origins (Figure 1).

The fact that gliomas histologically resemble glial cells initially suggested that they arose from glial progenitors: astrocytomas from astrocytic progenitor cells and oligodendrogliomas from oligodendrocyte progenitor cells (OPCs). However, recent studies have provided compelling evidence that high-grade astrocytomas arise from multipotent neural stem cells (NSCs). Conditionally deleting the tumor suppressors *NF1*, *p53*, and *PTEN* in NSCs—by activating a Nestin-Cre transgene or by injecting Cre viruses into the subventricular zone (SVZ)—induces malignant astrocytomas, whereas targeting the same mutations to the cortex or striatum fails to induce tumors (Alcantara Llaguno et al., 2009). Likewise, lentiviral transduction of oncogenic Ras and Akt into the SVZ or hippocampus causes astrocytomas, whereas nonneurogenic brain regions are resistant to transformation (Marumoto et al., 2009). These studies suggest that malignant astrocytomas originate from stem cells.

In contrast, the origins of oligodendroglioma remain controversial. The epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) pathways have both been implicated in the etiology of oligodendroglioma, and retroviruses encoding these ligands induce proliferation of stem cells in the SVZ and OPCs in the white matter (WM) (Assanah et al., 2006; Dai et al., 2001; Ivkovic et al., 2008). But the fact that the driving force for tumorigenesis in these studies is a secreted growth factor (which affects not only virally infected cells but also their neighbors) makes definitive identification of the cell of origin difficult.

To investigate the origin of oligodendrogliomas driven by cell-autonomous signals, Persson et al. (2010) used a model in which expression of an oncogenic EGF receptor (v-erbB) is driven by the human S100β promoter. S100β is expressed in OPCs committed to differentiate along the oligodendrocyte lineage. S100β-verbB transgenic mice develop low-grade oligodendrogliomas; when they are crossed to mice carrying mutations in p53, tumors occur with shorter latency and become more malignant. Persson et al. (2010) report that in these mice, the earliest signs of increased proliferation are seen in NG2+ OPCs in the WM and not in NSCs in the SVZ. Moreover, in contrast to astrocytoma cells, which frequently express NSC markers and exhibit multilineage differentiation, S100β-verbB tumor cells express markers of OPCs and differentiate almost exclusively into oligodendrocytes. Importantly, similar properties—localization near the WM, expression of OPC markers, and limited differentiation potential—are associated with human oligodendrogliomas. These findings suggest that oligodendrogliomas arise from OPCs rather than stem cells.

In addition to originating from stem cells, astrocytomas have been reported to contain stem-like tumor-initiating cells (TICs) that are critical for tumor propagation. Marked by expression of CD133 (Prominin1) or CD15 (SSEA-1), these cells form self-renewing neurospheres in vitro and give rise to tumors following transplantation (Bao et al., 2006; Son et al., 2009). To determine whether S100β-verbB oligodendrogliomas also contain TICs, Persson et al. (2010) fractionated tumor cells by flow cytometry and found that CD15+ tumor cells could form neurospheres but could not initiate tumors following transplantation. In contrast, OPC-like NG2+ cells, which showed limited neurosphere-forming ability, were enriched in tumorigenic potential. NG2+ cells from human oligodendroglioma were also highly tumorigenic. Thus, progenitor-like rather than stem-like cells are responsible for propagation of oligodendrogliomas.

High-grade astrocytomas are extremely resistant to radiation and chemotherapy, and this has been suggested to be due to intrinsic resistance of their TICs (Bao et al., 2006). Oligodendrogliomas are often more sensitive to therapy,

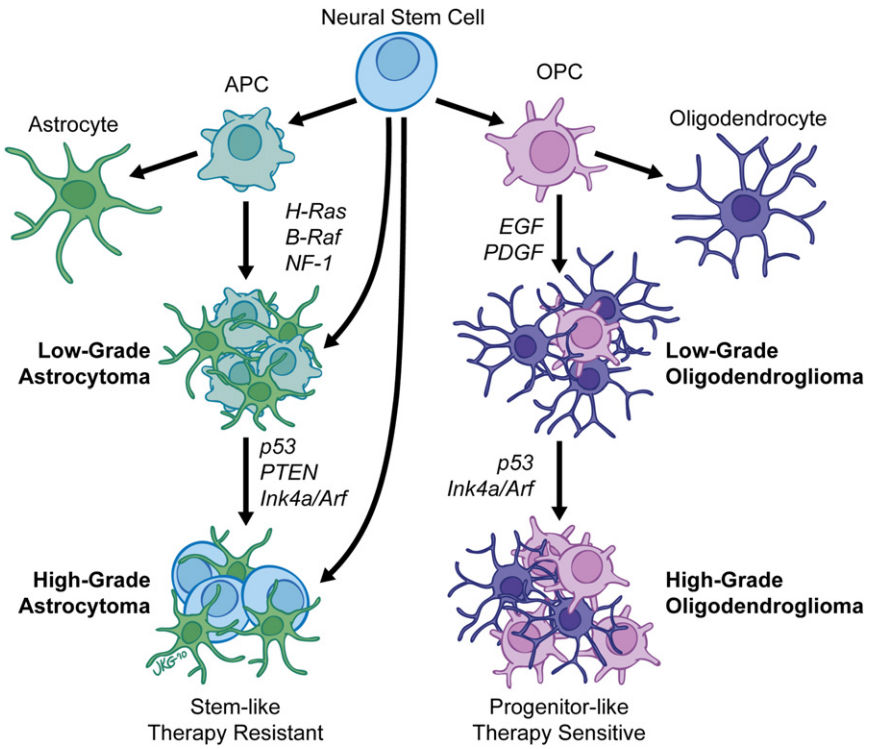

Figure 1. Cell of Origin and Oncogenic Mutations Collaborate to Determine Glioma Behavior
Activation of growth factor (EGF, PDGF) or Ras-MAP kinase (H-Ras, B-raf, NF-1) signaling pathways in neural stem cells (NSCs) or progenitors usually results in hyperplasia or low-grade gliomas; mutations in tumor suppressors (p53, PTEN, Ink4a/Arf) convert these to high-grade tumors. When genetic lesions are targeted to NSCs or astrocyte progenitors (APCs), the resulting tumors (astrocytomas) retain stem cell characteristics: multipotency, neurosphere formation, and resistance to therapy. When mutations are initiated in oligodendrocyte progenitors (OPCs), the resulting tumors (oligodendrogliomas) have characteristics of OPCs, including restricted differentiation, poor neurosphere formation and sensitivity to therapy. (Illustration by Jill Gregory.)

and Persson et al. (2010) hypothesized that this might be a property of the glial progenitors from which they arise. To test this, they treated progenitors, stem cells, astrocytomas, and oligodendrogliomas with temozolomide, an alkylating agent used for glioma therapy. Whereas normal NSCs and astrocytoma cells were largely resistant to the drug, normal OPCs and oligodendroglioma cells were markedly growth-inhibited. These studies demonstrate that TICs from oligodendroglioma, unlike their counterparts from astrocytoma, are therapy-sensitive.

The present study echoes previous reports that medulloblastomas can arise from, and be propagated by, progenitor-like cells (Read et al., 2009; Yang et al., 2008). These studies emphasize that the capacity for tumor initiation and propagation is not restricted to cells with stem cell characteristics. An important implication of this work is that in searching for novel approaches to therapy, we must carefully consider the nature of the tumor we are trying to target: just as normal progenitors and stem cells depend on distinct signals for their growth and survival, tumors derived from these cells may be driven by distinct signals and may require different approaches to therapy. Although stem cell-specific therapies are certainly worth developing, they may not be useful for all types of cancer.

The findings of Persson et al. (2010) elegantly demonstrate that v-erbB and p53 mutations can transform OPCs into oligodendrogliomas. But it is interesting to consider what would happen if the same oncogenic events were induced in multipotent NSCs: would the stem cells simply differentiate into OPCs and give rise to the same type of tumor (as was reported for medulloblastoma [Yang et al., 2008]) or would targeting these lesions to stem cells result in astrocytoma, as has been seen with oncogenic Ras and Akt or with loss of NF1, p53, and PTEN (Alcantara Llaguno et al., 2009; Marumoto et al., 2009). It is tempting to speculate that the cell of origin dictates the phenotype of a tumor (astrocytic or oligodendroglial) and that the oncogenic mutations it contains determine its grade or aggressiveness. But given the propensity of some signals to induce dedifferentiation (Dai et al., 2001), the truth is likely to be more complicated. In the end, the properties of a tumor are likely to depend on the mutations that drive cell growth and survival as well as the cellular context in which these mutations take place. Knowing where a stranger comes from can certainly tell you a lot about their character, but checking if they have a criminal record may also help: even good families occasionally have malignant children.

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