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Glioma Development: Where Did It All Go Wrong?

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Investigating the family tree of a tumor to identify its cellular origins is a daunting task. Liu et al. (2011) now use an elegant lineage tracing technique (MADM) to visualize glioma from its earliest stages. They show that mutations originally induced in neural stem cells lie dormant and only trigger malignant transformation following differentiation into oligodendrocyte precursor cells.

By the time a tumor has grown large enough to be detected, it is often too late to establish with any certainty how it came to be there. Although cancer genomics is providing impressive insights into the mutations that drive cancer progression, it is not yet possible to use this information to "rewind" tumor development and establish exactly how (which mutation) and where (in what cell type) the first steps toward cancer occurred. In this issue of *Cell*, Liu et al. take the reverse approach, using a transgenic cell-labeling system known as mosaic analysis with double markers (MADM) to track tumor growth in an inducible mouse glioma model (Liu et al., 2011). Their results highlight the subtle but important distinction between where a mutation occurs (cell of mutation) and where it drives tumor development (cell of origin).

Glioma is the most common form of primary brain tumor and includes morphologically distinct cancers such as astrocytoma, ependymoma, and oligodendroglioma. This heterogeneity has led many to suggest that driving mutations might occur in the respective differentiated cell types. In support of this possibility, genetically engineered mouse models have been used to demonstrate that platelet-derived growth factor (Pdgf) overexpression in conventionally non-neurogenic niches results in glioma formation (Hambardzumyan et al., 2009). In addition, Pdgf overexpression in committed progenitors, such as oligodendrocyte precursor cells (OPCs), also initiates tumors (Lindberg et al., 2009). These results are further supported with data demonstrating that astrocytomas can develop outside of proliferative niches when mutations in Pten, p53, and Rb pathways are combined, as well as another study showing that activation of wild-type and/or mutant Egfr combined with ablation of tumor suppressor gene function in the adult mouse striatum results in glioma formation (Chow et al., 2011, Zhu et al., 2009).

An alternative but not mutually exclusive possibility for the origin of cancer is that a mutated tissue stem cell could directly give rise to distinct tumor lineages depending on the nature of the affected signaling pathway (Visvader, 2011). Neural stem cells (NSCs) are likely candidates for the cell of origin of glioma due to their long lifetime, self-renewal, and sustained proliferative capacity, as well as commonalities with cancer stem cells, which are defined by their ability to propagate complex tumors when implanted into a host (Singh et al., 2004). In support of this hypothesis, introduction of mutations associated with human brain tumors into NSCs generates murine gliomas in anatomical locations consistent with a stem cell origin, such as the subventricular zone (Alcantara Llaguno et al., 2009; Wang et al., 2009; Zhu et al., 2005).

Liu et al. address this debate by tracing the growth of individual lineages descended from a mutated NSC (Liu et al., 2011). In their system, Cre-mediated recombination in dividing NSCs inactivates both p53 and Nf1 tumor suppressors while simultaneously activating the expression of a green fluorescent protein (GFP) tracer. Alternative recombination results in wild-type p53 and Nf1 but activates expression of red fluorescent protein (RFP); nonrecombined cells remain heterozygous null for both genes and lack a fluorescent label (Figure 1A). As such, Liu et al. discriminate between cells with oncogenic mutations (green) and normal counterparts (red) over time. Both wild-type and mutant NSCs give rise to the expected repertoire of neuronal and glial cell types. However, only mutant NSCs give rise to hyperproliferative oligodendrocyte precursor cells (OPCs) that eventually develop into malignancies with varied histological features. All other NSC-derived cell types, including NSCs themselves, remain mostly unaffected by disruption of the two tumor suppressive pathways. Finally, when p53/Nf1 inactivation is targeted specifically to OPCs, tumors form that are essentially identical to NSC-derived gliomas (Figure 1B). Interestingly, these tumors acquired the expression of NSC genes, which could be misleading were it not for the earlier analysis of cell lineages.

The findings demonstrate that, in p53/Nf1 mutation-driven glioma, mutation may initially occur in either NSCs or OPCs, but only OPCs provide the suitable cellular context needed for transformation. The importance of cellular context in determining the outcome of a mutation is also illustrated by inherited cancer syndromes in which individuals harbor oncogenic mutations in every cell but develop tumors in only a small number of tissues (such as *BRCA1* mutations in

breast cancer). Though many cancer types share common genetic lesions, there is often an association of specific genetic changes with restricted cancer types (for example, the *BCR-ABL* fusion in chronic myelogenous leukemia). By highlighting the role of differentiation state in determining the outcome of a particular mutation, Liu et al. reconcile the debated potential of both stem cells and lineage-committed precursors as cellular targets in cancer initiation.

It is not yet clear to what extent the lineage specificity of p53/Nf1 mutations is conserved between mouse and man. For example, comparative oncogenomics of the mouse model tumors matches them with human proneural glioblastomas, which are associated with aberrant PDGFR signaling. In contrast, NF1 mutations in human glioblastomas typically correlate with the mesenchymal subtype (Phillips et al., 2006). This caveat withstanding, the work will undoubtedly focus attention on OPCs as targets for glioma investigators, devising new means to halt cancer progression, especially for treatment-refractory tumors. We should also be open to the possibility that distinct glioma subtypes may be driven by different cells of origin, and future studies taking advantage of MADM will be required to determine whether OPCs are also the cell of origin in gliomas with different driving mutations, genetic backgrounds, and age at the time of mutation. Finally, this powerful technique will likely be applied to other tumor types and could provide a useful tool not only to identify cell of origin, but also to rigorously evaluate new methods for detecting the earliest stages of cancer.

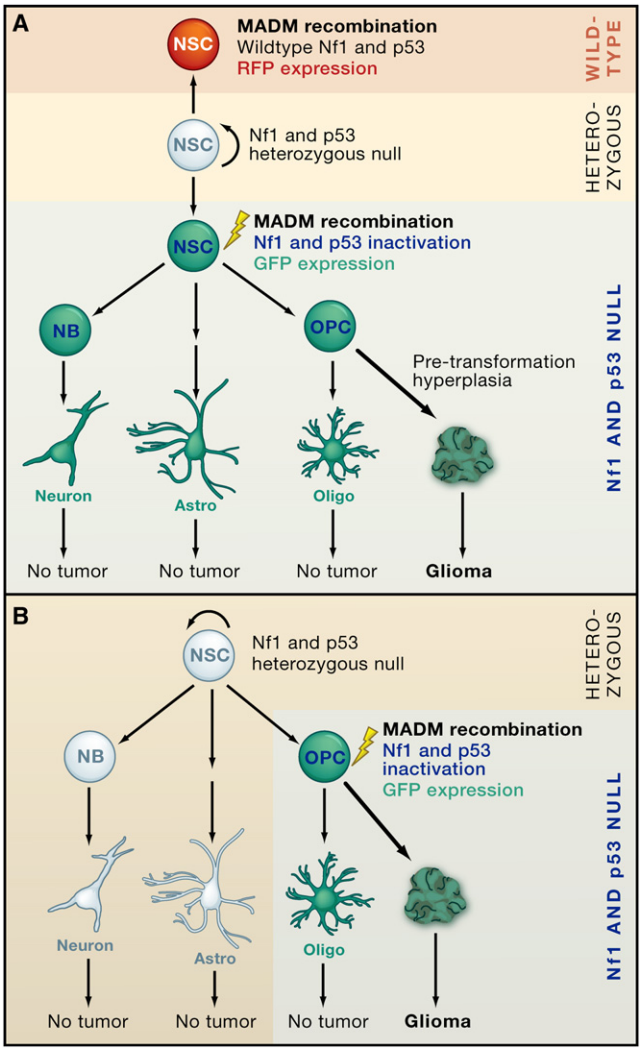

Figure 1. MADM Identifies Cell of Origin in Glioma

(A) The hierarchy of NSC differentiation. MADM recombination in dividing NSCs resulting in p53/Nf1 inactivation also labels mutant cells with GFP. RFP-labeled cells undergo alternative recombination to become wild-type for p53 and Nf1. Despite a shared genetic background in all mutant NSC-derived lineages, only OPCs expand and give rise to glioma.

(B) Gliomagenesis also occurs when p53/Nf1 inactivation is targeted specifically to OPCs. These experiments also demonstrate that the cell of mutation may or may not be distinct from the cell of origin in glioma.

NSC, neural stem cell; NB, neuroblast; OPC, oligodendrocyte precursor cell; Astro, astrocyte.

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