



Can One Cell Influence Cancer Heterogeneity?

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Science **338**, 1035 (2012);

DOI: 10.1126/science.1231594

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bility, macroporosity, release of entrained ash, and labile carbon (9–11).

To understand the long-term value of biochar addition for both soil improvement and carbon storage, methods to assess and predict biochar durability and changes in its properties are required. Beyond real-time observation (12) and experimental manipulation (13), insight can be gained from the study of old wildfire charcoal as a naturally aged analog (14). Focusing effort toward these strategic goals could later explain much-studied but less predictable effects on native soil carbon (priming) and nitrous oxide emission.

Positive effects on soils and crop production cannot alone confirm the viability of producing and deploying biochar, however. In many situations, there will be limited technology options for pyrolysis and constraints on affordable or available feedstock (2). Strategies for deploying biochar must also consider the practical and logistical issues of storage, transport, and incorporation into soil.

Doses of application should reflect such constraints. In the United Kingdom, for example, the projected break-even cost of deploying biochar from fresh or clean waste biomass exceeds \$150/t, suggesting that only annual doses at the lowest experimental rates would currently be economic (15). Understanding the relative merits of regular low-

dose applications as part of a nutrient management regime, versus larger one-off applications, is therefore a priority; establishing protocols for the safe use of biochar derived from low-cost waste streams is another.

Future applications may include broad-acre crops, high-value vegetable production, and management of liquid manures, and there is already niche usage in horticultural growing media and fertilizer products. Such diverse modes and scales of deployment require a generalized understanding of biochar function. Using biochar to enhance existing products, even as a relatively minor ingredient, could build familiarity and reliable supply chains for potential future scale-up. Other functions of biochar worthy of consideration include provision of compounds that promote plant growth and resistance to disease (16, 17) or the modification of nutrient dynamics at the plant-soil interface (18). There may also be synergistic effects between biochar and manure (19), compost, and fertilizer.

Integrated understanding of biochar function and deployment will support expanding use patterns that are economic and environmentally attractive. Over decades, the use of biochar could create soils that in management and function begin to resemble the fertile terra preta (famed charcoal-rich soils in Amazonia). Full realization of these benefits

requires rewards and incentives at a national level that reflect the global value of both agriculture and climate.

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Acknowledgments: The UK Biochar Research Centre (UKBRC) was established in 2009 under a Science and Innovation funding award to S. Haszeldine by the Engineering and Physical Sciences Research Council, with additional funding from the Scottish Funding Council and the University of Edinburgh. Discussions with all UKBRC colleagues are acknowledged in particular S. Shackley and O. Mašek.

10.1126/science.1225987

CANCER

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Gliomas are the most common form of malignant brain tumor in adults and have generally poor clinical outcomes. Patients with the most aggressive form of glioma, glioblastoma multiforme (GBM), have a low 5-year survival rate (1). Progress has been made in characterizing the genetic lesions and cells of origin in GBM, both of which may contribute to disease pathogenesis. On page 1080 in this issue, Friedmann-Morvinski *et al.* (2) show that differentiated neuronal cells and glial cells in the mouse brain can revert to less mature states upon acquiring these genetic lesions. Thus,

multiple different cell types in the central nervous system, and not just neural stem cells, can be transformed into GBM in an animal model that recapitulates important aspects of the human disease.

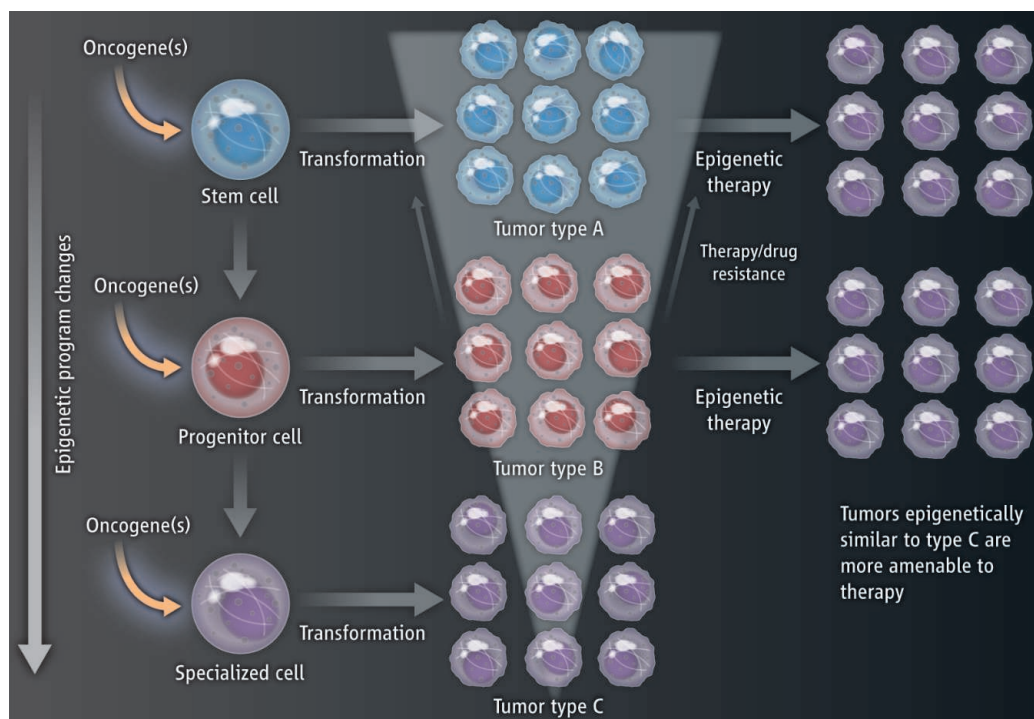
The cellular background (the chemical modifications of chromatin, or the epigenetic state) in which a transforming genetic lesion occurs (cell of origin) may contribute to the complexity of cancer. The potential importance of the cell of origin and the transformability of multiple cell types raises questions about hierarchical relationships between cells and the properties of tumor-initiating cancer stem cells (thought to be cells within a tumor that can self-renew and give rise to heterogeneous populations of cancer cells that constitute the tumor). In mouse models of glioblas-

Genetic lesions allow mature brain cells in mice to revert to immature forms that can give rise to tumors.

toma, genetic lesions introduced in both neural stem cells and more mature glial cells may lead to tumor formation (3, 4). Although glial progenitor cells and differentiated astrocytes both have the potential to contribute to GBM, the tumors develop differently, depending on the cell of origin (5). Specific subtypes of human GBM show some relation to normal brain cell types (6) based on gene expression, suggesting that the cell of origin may influence the final GBM subtype.

Friedmann-Morvinski *et al.* examined this possibility in mice using a highly targeted method (stereotaxic injection of lentivirus vectors into cells that allows transduction of oncogenes or deletion of tumor suppressor genes) to induce genetic lesions in specific central nervous system cell types in vivo. The

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Cell of origin. Cellular differentiation and specialization are accompanied by gradual changes in epigenetic programs. Genetic lesions can initiate tumorigenic transformation of tissue stem cells, differentiated progenitors, and more specialized cells. The cell of origin may influence the epigenetic state of the resulting tumor. Cancers expressing stem cell programs have an adverse prognosis. Modulating the epigenetic state of more aggressive tumors (epigenetic therapy) may sensitize them to treatment with current therapies.

authors demonstrate that multiple normal cell types within the central nervous system can be transformed into tumors, consistent with findings that multiple hematopoietic cell types can be transformed in leukemia development (7, 8). However, which hematopoietic cell types can be transformed is determined by the initiating oncogene, demonstrating an interaction between the epigenetic state of the cell of origin and the initiating oncogene (9, 10). The study by Friedmann-Morvinski *et al.* indicates that both neuronal and glial cells, upon loss of the tumor suppressor proteins p53 and neurofibromatosis-1 (NF1), reactivated expression of markers normally found in immature cells of the nervous system. The transformed cells expressing the immature markers then gave rise to tumors. Therefore, cancer cells may not follow the same strict relationships and directionality that normal cells follow during lineage development.

The finding of Friedmann-Morvinski *et al.* does not rule out a hierarchical relationship between cells in a fully developed cancer, with some cells being more tumorigenic than others. However, if more differentiated cells can be transformed and revert to more immature states, markers of normal differentiation will not consistently identify the most tumorigenic populations. Indeed, mouse models of

leukemia have demonstrated this possibility (11). Therefore, markers that are inextricably linked to cellular signaling pathways that control extensive cancer cell proliferation and self-renewal should be more predictably associated with tumor-initiating potential than markers associated with normal differentiation. However, most studies assessing cellular permissiveness to transformation have been performed on mouse cells, which are easier to transform than human cells. Further studies are required to define the permissiveness of various human cell types. Furthermore, studies such as that of Friedmann-Morvinski *et al.* introduce multiple genetic abnormalities simultaneously, so mutations could accumulate in tissue-specific stem cells until the final lesion necessary for tumor development is acquired in one of many transformable cell types; that cell type then becomes the cell of origin for that cancer.

The genetic makeup of a malignancy correlates with clinical outcome and can therefore be useful in predicting prognosis and planning treatment. In addition to the impact of the genetic lesions themselves, the epigenetic state of cells within the cancer, perhaps influenced by the cell of origin, likely contributes to the clinical properties, including drug resistance (12). Gene expression profiling of

multiple different types of cancer have identified different subtypes that are not clearly defined by genetic abnormalities, and thus may be defined by epigenetic mechanisms (13). Indeed, Friedmann-Morvinski *et al.* show that specific subtypes of mouse GBM are developed on the basis of the cell of origin. Further studies are required in multiple cancers to determine the extent to which the cell of origin influences epigenetic heterogeneity.

As our understanding of cancer genetics broadens, the opportunities to apply that knowledge to individualize therapy for cancer patients with more targeted therapies will continue to increase as well. However, molecularly targeted therapies have shown that cancers are remarkably adept at developing resistance, and some of the mechanisms of resistance are likely a result of either pre-existing (cancer stem cells) or acquired (adaptation) epigenetic differences. These studies raise the possibility that influencing the epigenetic state of cancer

cells may sensitize cancers to concurrent treatments and/or restrict cancer cell adaptation to therapeutic intervention (see the figure). Emerging classes of therapeutics aimed at enzymes that catalyze chemical modifications of DNA and chromatin-associated proteins (and thereby modify the epigenetic states of cells) are currently entering clinical trials (14). There is hope that a combination of therapies that target genetic abnormalities, epigenetic properties, immune mechanisms, and resistance to programmed cell death (apoptosis) will usher in better treatments to deal with difficult-to-cure cancers like GBM.

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