

Immunotherapy

Major finding: Inflammation-driven reversible dedifferentiation of melanoma cells impairs recognition by CTLs.

Mechanism: TNF- α promotes loss of melanocytic antigens and expression of the neural crest marker NGFR.

Impact: Targeting of both melanocytic and nonmelanocytic antigens is necessary for successful therapy.

MELANOMA CELL PLASTICITY MEDIATES RESISTANCE TO ADOPTIVE CELL THERAPY

Adoptive T-cell transfer of CD8-positive, tumor antigen-specific cytotoxic T lymphocytes (CTL) induces tumor regression in patients with metastatic melanoma. However, these responses are not durable, and tumors frequently reoccur due to acquired resistance to CTL therapy. To identify the mechanisms underlying this resistance, Landsberg and colleagues used a mouse model of melanoma driven by overexpression of hepatocyte growth factor and oncogenic mutant cyclin-dependent kinase 4 together with an adoptive T-cell transfer protocol that recapitulated the tumor regression, remission, and relapse observed in patients with melanoma. In addition to reduced T-cell effector function, a subset of relapsed tumors in these mice exhibited increased immune cell infiltration and loss of melanocytic differentiation antigens such as gp100, resulting in diminished tumor recognition by melanoma antigen-specific CTLs and suggesting that these tumors may have undergone dedifferentiation. In support of this idea, pigmentation gene expression was reduced in relapsed tumors and was accompanied by upregulation of immune-response and mesenchymal genes, as well as induction of the neural crest marker nerve growth

factor receptor (NGFR). Intriguingly, this process was reversible, as gp100 expression and CTL recognition were restored *in vivo* in retransplanted tumor cells but were subsequently reduced again in tumors that developed resistance. These changes in gene expression were dependent on immune-cell-derived TNF- α secretion, which stimulated NGFR and reduced gp100 expression, whereas inhibition of TNF- α enhanced gp100 expression and tumor recognition by CTLs. Importantly, TNF- α induced a similar dedifferentiated phenotype in human melanoma cell lines and resulted in selective impairment of tumor cell recognition by melanoma-specific CTLs compared with CTLs specific for nonmelanocytic antigens. These results implicate dynamic changes in tumor differentiation status induced by the inflammatory microenvironment as a mechanism of resistance to adoptive T-cell transfer and suggest strategies to improve the clinical efficacy of this therapy. ■

Landsberg J, Kohlmeyer J, Renn M, Bald T, Rogava M, Cron M, et al. Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. Nature 2012;490:412–6.

Tumorigenesis

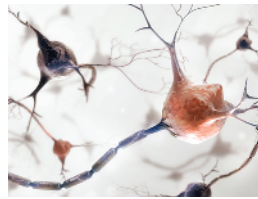
Major finding: RAS activation and p53 loss induce dedifferentiation of mature cells into tumor-initiating cells.

Clinical relevance: Astrocyte and neuron-derived tumors resemble the mesenchymal GBM subtype.

Impact: Brain cell plasticity, not a distinct population of cancer stem cells, may underlie gliomagenesis.

GLIOBLASTOMA CAN ARISE FROM DIFFERENTIATED CELLS

Genomic analyses have facilitated the classification of glioblastoma multiforme (GBM) into several molecular subtypes, but our understanding of the etiology of this heterogeneous group of tumors remains extremely limited. The identification of tumor-initiating cells expressing stem and progenitor cell markers in GBM has led to the theory that cells with intrinsic stem-like properties underlie GBM initiation and recurrence. However, Friedmann-Morvinski and colleagues report that dedifferentiation of mature cells can also lead to GBM formation. Simultaneous p53 inactivation and activation of the RAS pathway, either by neurofibromin 1 (NF1) inactivation or mutant HRAS expression, in the neurons or astrocytes of transgenic mice using Cre recombinase-inducible lentiviral vectors led to the formation of high-grade gliomas regardless of the site of injection. Limiting dilutions of primary cortical neurons or astrocytes that were lentivirally transduced *in vitro* and transplanted into recipient mice also formed high-grade gliomas that expressed high levels of neural progenitor markers, further indicating that terminally



differentiated cells could undergo transformation and act as tumor-initiating cells. Consistent with a paradigm in which oncogenic insults lead mature cells to acquire the capacity to dedifferentiate into neuroprogenitor-like pluripotent cells, primary cortical neurons and astrocytes transduced with both mutant *HRAS* and *p53* short hairpin RNA changed morphology and formed neurosphere-like structures, whereas untransduced cells, cells only lacking p53, or cells only expressing mutant *HRAS* remained astrocytes. Of note, the expression signatures of the neuron- and astrocyte-derived gliomas resembled those of human mesenchymal-subtype GBMs, in which inactivating mutations of *NF1* and *TP53* are sometimes found, suggesting that a similar phenomenon may occur in human brain tumors. ■

Friedmann-Morvinski D, Bushong EA, Ke E, Soda Y, Marumoto T, Singer O, et al. Dedifferentiation of neurons and astrocytes by oncogenes can induce gliomas in mice. Science 2012 Oct 18 [Epub ahead of print].