



Brain cells' hidden differences linked to potential cancer risk

By Michael Purdy

Feb. 19, 2009 -- Brain cells long lumped into the same category have hidden differences that may contribute to the formation of tumors, according to a new study from researchers at Washington University School of Medicine in St. Louis. Scientists showed that brain cells known as astrocytes make use of different genes depending on what region of the mouse brain they came from. These differences are too subtle to overtly mark them as distinct cell types, but substantial enough to make it easier for the cells to multiply more in response to genetic changes that increase cancer risk.

"We've shown that identical-looking astrocytes from different brain regions are genetically distinct, and these molecular differences may alter the risk for cancer development," says senior author David H. Gutmann, M.D., Ph.D., the Donald O. Schnuck Family Professor of Neurology. The finding appears online in the journal *Glia*.

In recent years, Gutmann has shown that the transition from a normal to a cancerous cell is heavily influenced by factors outside the cell, such as growth factors and other signals from neighboring cells. He calls the new finding the "yin" to the earlier research's "yang."

According to Gutmann, these dual lines of research show that there are two factors that explain why tumors form in some brain regions and not in others. First, the cell must live in a brain region that provides the right environmental signals to facilitate tumor formation. Second, as revealed by the new research, the cell itself also must be responsive to those environmental signals. "In this regard, tumor formation and growth requires both a permissive environment and a receptive cell type," Gutmann says.

All of the body's cells have the same genes, but different cell types turn genes on and off or use certain genes more or less often. These patterns of activating and inactivating genes both allow cells to grow and develop into specialized structures and to take on specialized roles at the level of individual cells.

To gain insights into the significance of potential genetic differences between astrocytes from different brain regions, Gutmann and his colleagues used a mouse model of a common inherited cancer syndrome, neurofibromatosis type 1 (NF1). In children with NF1, brain tumors typically arise in the optic nerve and brainstem and only rarely appear in the cortex. The condition is caused by a mutation in a gene known as the neurofibromatosis 1 gene.

When Gutmann and post-doctoral researcher Tu-Hsueh Yeh, M.D., Ph.D., examined astrocytes from different brain regions under the microscope and in other standard tests, the astrocytes looked similar. But when the researchers analyzed gene activity levels — which genes the cells used to make proteins and how often they were used — sharp differences became apparent. For example, astrocytes from the cortex have low levels of neurofibromatosis-1 gene expression compared to astrocytes from the optic nerve or brainstem.

In addition, when they disabled the neurofibromatosis 1 gene in cell culture and in the mouse brain, they found what Gutmann called "dramatically increased" growth in astrocytes from the brainstem and optic nerve. In contrast, the same change had no effect on growth of astrocytes from the cortex.

"These exciting results suggest that not all astrocytes are the same, and that genetic differences between astrocyte populations may partly dictate where brain tumors form in children with NF1," says Gutmann. "Future studies aimed at understanding the complex interplay between environmental signals and receptive cell types may lead to an improved understanding of brain tumor formation and help us customize our treatments in ways that improve their effectiveness."

Yeh T-H, Lee DY, Gianino SM, Gutmann DH. Microarray analyses reveal regional astrocyte heterogeneity with implications for neurofibromatosis type 1-regulated glial proliferation. *Glia*, online February 3, 2009.