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Presentation Title: Neural stem cells, brain tumors, and brain tumor stem cells

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Neural stem cells are self-renewing and multipotent capable of producing the three major cell types of the brain: neurons, astrocytes and oligodendrocytes. It has long been postulated that neural stem cells are the cells of origin for many brain tumors. Many brain tumors express markers traditionally associated with neural stem cells and also have multiple cellular phenotypes. Additionally, neural stem cells overexpressing oncogenes can form brain tumors in vivo (e.g. Holland et al., 2000).

We (Hemmati et al., 2003) and other groups (Ivanatova et al., 2002, Singh et al., 2003) have isolated cells from brain tumors that have many of the characteristics of neural stem cells, including the ability to form spheres in response to mitogenic stimulation, to self-renew and to produce multiple phenotypes that are typical of the brain tumors of origin. These cells can act as tumor founding- or tumor stem cells, since, upon transplantation into immunodeficient rodent brain, they form tumors which also contain the same types of progenitors (Galli et al., 2004; Singh et al., 2004). Initial expression analysis demonstrates that tumor-derived progenitors share many genes in common with neural stem cells, including many that we have identified from genetic screens of mouse neural stem cells using a combined genetic subtraction and microarray approach. Further genomic analysis demonstrates a scale free topology to glioma gene expression with several functional modules of interrelated genes. Many of the genes co-expressed by brain tumors and neural stem cells are identifiable as cell cycle "hub" genes and thus may be critical regulatory components of brain tumor proliferation. Furthermore, these co-expressed genes are associated with states of enhanced neural stem cell self-renewal.

Functional analysis in vitro demonstrates that at least some of these genes play important roles in the proliferation of brain tumor-derived cell lines as well as brain tumor-derived progenitors. One of these genes, MELK, is a serine-threonine kinase of the snf1/AMPK family with a previously unknown function. MELK is highly expressed in glioblastoma multiforme, astrocytomas, ependymomas and medulloblastomas. It is expressed in the developing neuroepithelium in vivo and is a marker for self-renewing neural stem cells as well as proliferating, self-renewing granule cell precursors. Studies using RNA interference show that MELK regulates neural stem cell self-renewal as well as the proliferation of medulloblastoma cell lines and tumor-derived progenitors. These data, along with those of other groups support the hypothesis that the study of neural stem cell self-renewal will reveal important targets for brain tumor therapy.

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