

The Low-Grade Oligodendroglioma Brain Tumor Research Grant

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Tumorigenic potential of progenitor cells in low-grade oligodendrogliomas.
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Abstract

Understanding the progenitor or stem cells that give rise to oligodendrogliomas would have significant impact on the development of new treatment strategies. Recent studies have pointed to 2 distinct populations of cycling cells in the adult brain that may give rise to human gliomas; 1) neural stem cells (NSC) in the SVZ and 2) oligodendroglial progenitor cells (OPCs) that are widely distributed throughout the brain (Assanah et al., 2006; Jackson et al., 2006). Most studies have focused on high-grade gliomas, however the cell of origin for low-grade oligodendrogliomas is not known. We hypothesize that oligodendrocyte progenitors in the adult white matter are the cells that give rise to low-grade oligodendrogliomas. This hypothesis is derived from several important observations: 1) Oligodendroglioma cells share many antigenic markers of OPCs, including olig2, NG2, and PDGFR . 2) OPCs are the largest population of cycling cells in the adult brain and far outnumber the relatively small number of NSC found in the SVZ. 3) Oligodendrogliomas most commonly occur in the subcortical white matter where OPCs are most abundant. The goal of this study is to isolate subpopulations of cells from human oligodendrogliomas and test their ability to give rise to tumors when transplanted into the brains of nude mice. We will use fluorescence activated cell sorting (FACS) of cells using 2 well-characterized cell surface markers: CD133 (which is a marker for NSC) and O4 (which is a marker for OPCs). In our preliminary studies using flow cytometry of O4 and CD133, we have found that low-grade oligodendrogliomas contain a large population of O4+ cells (70-95%) whereas CD133+ cells compose a relatively small population (0.1-5%). Interestingly, the vast majority of these CD133+ cells are also O4+. To expand on these findings we will continue to FACS sort oligodendrogliomas for expression of O4 and CD133, collecting single positive, double positive and double negative populations. We are particularly interested in comparing the tumorigenic potential of CD133+/O4+ and CD133-/O4+ cells. To track their course, these populations will be labeled in vitro with GFP (CD133+/O4+) or DsRed (CD133-/O4+) expressing lentivirus and then stereotactically injected into the brains of adult nude mice (alone or in combination) and their fate and tumorigenicity determined in vivo. Dilution studies will be performed to determine the minimum number of cells needed to form tumors from each group. The resultant tumors will be analyzed histologically and immunohistochemically to determine the type and grade of the tumors and to characterize the phenotype of the cells that compose the tumor. The retroviral reporters (GFP and DsRed) will also allow us to compare the tumorigenic potential of the different populations within the same xenograft tumor.

Previous studies with glioblastomas have shown that CD133+ cells are uniquely tumorigenic. Extrapolating from these previous studies, one might predict that CD133+/O4+ cells would be the only population capable of forming tumors. If this proves to be the case, it would point to a very small population (less than 5%) of cells that needs to be targeted. If it turns out that CD133-/O4+ cells have the capacity to form tumors, this could lead to the identification of a novel form of cancer stem cell that is derived from or closely related to OPCs. After tumors form in the nude mice, the virally labeled cells can be FAC sorted from the xenografts and reinjected into a second generation of nude mice. These serial transplantation studies would allow us to test an important prediction of the cancer stem cell hypothesis: that cancer stem cells give rise to more differentiated progeny which account for the bulk of a tumor mass but which have a limited capacity to self-renew and therefore have lost their tumorigenic potential (Singh et al., 2004). If, for example, CD133 proves to be the uniquely tumorigenic cells in some (or all) low grade oligodendrogliomas, then the resultant xenografts from GFP tagged CD133+/O4+ cells should include large numbers of GFP+ CD133- cells (the progeny). If these xenografts are resorted on GFP and CD133, then the CD133+/GFP+ and not the CD133-/GFP+ should form tumors when reinjected into second-generation recipients and the resultant tumors should again behave the same way. Thus, these experiments will not only test tumorigenic potential of subpopulations within low-grade oligodendrogliomas, they may also validate one of the most interesting and important implications to the cancer stem cell hypothesis.