

The Low-Grade Oligodendroglioma Brain Tumor Research Grant

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Targeting CD24 in oligodendroglioma tumor progenitor cells

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Abstract

Tumors may arise from the dysregulation of endogenous progenitor or stem cells. Neural stem and progenitor cells have recently become a focus for brain tumor biology as these cells remain mitotically competent throughout the life of an individual and are, as such, targets for neoplastic mutations. To identify neoplastic changes causal in transformation of resident progenitor and stem cells, we have taken a genomics approach whereby neoplastic stem and progenitor cells are directly compared to their native, noncancerous homologues. Unlike previous brain tumor genomics studies which have relied upon bulk tissue profiling of whole tumors, our approach permits the identification of genes specifically expressed by the oncogenic progenitor cells. We have shown the utility of this strategy in our initial studies on neurocytoma, a rare tumor of ventricular zone (VZ) neuronal progenitors (Sim et al., *J Neurosci.*, 2006). The expression of neurocytoma was normalized against that of sorted human VZ progenitors. We identified dysregulation of IGF2 signaling, the importance of which was confirmed by the observed loss of IGF2 imprinting in neurocytoma. In preliminary studies, we have expanded this approach to oligodendrocytic tumors. We have used the ganglioside epitopes recognized by monoclonal antibody A2B5, which we have found identifies normal glial progenitor cells in the adult human brain (e.g. Nunes et al., *Nature Med.*, 2003; Windrem et al., *Nature Med.*, 2004; Sim et al., *Ann. Neurol.*, 2006), to separate A2B5 expressing tumor oligodendrocyte progenitor cells (OPCs) from both low and high grade oligodendrogliomas and mixed oligoastrocytoma. We compared the expression profiles of these isolated, purified tumor progenitors to the normal A2B5+ OPCs sorted from non tumor adult white matter. By this strategy, we identified a small set of functionally relevant genes specific to the OPC tumor progenitor. Among these few, we identified CD24, a selectin ligand that typically mediates developmental cell migration, as significantly overexpressed in A2B5 defined tumor progenitors relative to normal progenitors. The importance of CD24 overexpression in oligodendroglioma was reinforced by high CD24 levels observed in other central brain tumors in neurocytoma relative to the nest in sorted neuronal progenitors (Sim et al., *J. Neurosci.*, 2006). Moreover, in a parallel study of musashi sorted tumor progenitors in astrocytoma in which we used FACS to isolate tumor progenitor cells expressing the notch regulator musashi, we independently identified CD24 as a highly differentially expressed tumor transcript. Together these data suggest a direct involvement of CD24 in glioma progenitor growth and survival. In this proposal we seek to characterize the role of CD24 in the generation of oligodendroglioma tumor progenitors from

native oligodendrocyte progenitors. The following questions constitute our specific aims:

1. Is CD24 necessary for A2B5+ tumor progenitor self renewal?

Besides its role in tissue migration, CD24 has been implicated in the expansion competence of breast cancer. Does CD24 subserve a similar function in glioma?

2. Does lentiviral shRNAi knock down prevent parenchymal invasion of CD24 null tumor progenitor cells following orthotopic transplantation?

We expect that each aim will run concurrently. Initial setup will require 13 months for vector construction and lentiviral RNAi validation. In vitro knock down experiments will require 36 months and the tumor progenitor graft study will take 6 months. By these strategies, we hope to define the role of CD24 in oligodendroglioma tumorigenesis and identify possible strategies for oligodendroglioma treatment.