Targeting Cancer Stem Cells through L1CAM Suppresses Glioma Growth

Shideng Bao\textsuperscript{1,5,6}, Qiulian Wu\textsuperscript{1,5}, Zhizhong Li\textsuperscript{1,5}, Sith Sathornsumetee\textsuperscript{1,5}, Hui Wang\textsuperscript{1,5}, Roger E. McLendon\textsuperscript{2,5}, Anita B. Hjelmeland\textsuperscript{1,5} and Jeremy N. Rich\textsuperscript{1,3,4,5}

Departments of \textsuperscript{1} Surgery, \textsuperscript{2} Pathology, \textsuperscript{3} Medicine, and \textsuperscript{4} Pharmacology and Cancer Biology, and \textsuperscript{5} Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, North Carolina; and \textsuperscript{6} Departments of Radiation Oncology and Neurosurgery, University of Colorado Denver School of Medicine, Aurora, Colorado

Requests for reprints: Jeremy N. Rich, Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, P.O. Box 2900, Durham, NC 27710. Phone: 919-681-1693; Fax: 919-684-6514; E-mail: rich0001@mc.duke.edu and Shideng Bao, Departments of Radiation Oncology and Neurosurgery, University of Colorado Denver School of Medicine, P.O. Box 6511, Mail Stop 8123, Aurora, CO 80045. Phone: 303-724-0166; Fax: 303-724-1554; E-mail: shideng.bao@uchsc.edu.

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Malignant gliomas are lethal cancers that display striking cellular heterogeneity. A highly tumorigenic glioma tumor subpopulation, termed cancer stem cells or tumor-initiating cells, promotes therapeutic resistance and tumor angiogenesis. Therefore, targeting cancer stem cells may improve patient survival. We interrogated the role of a neuronal cell adhesion molecule, L1CAM, in glioma stem cells as L1CAM regulates brain development and is expressed in gliomas. L1CAM\textsuperscript{+} and CD133\textsuperscript{+} cells cosegregated in gliomas, and levels of L1CAM were higher in CD133\textsuperscript{+} glioma cells than normal neural progenitors. Targeting L1CAM using lentiviral-mediated short hairpin RNA
(shRNA) interference in CD133⁺ glioma cells potently disrupted neurosphere formation, induced apoptosis, and inhibited growth specifically in glioma stem cells. We identified a novel mechanism for L1CAM regulation of cell survival as L1CAM knockdown decreased expression of the basic helix-loop-helix transcription factor Olig2 and up-regulated the p21\(^{\text{WAF1/CIP1}}\) tumor suppressor in CD133⁺ glioma cells. To determine if targeting L1CAM was sufficient to reduce glioma stem cell tumor growth \textit{in vivo}, we targeted L1CAM in glioma cells before injection into immunocompromised mice or directly in established tumors. In each glioma xenograft model, shRNA targeting of L1CAM expression \textit{in vivo} suppressed tumor growth and increased the survival of tumor-bearing animals. Together, these data show that L1CAM is required for maintaining the growth and survival of CD133⁺ glioma cells both \textit{in vitro} and \textit{in vivo}, and L1CAM may represent a cancer stem cell–specific therapeutic target for improving the treatment of malignant gliomas and other brain tumors. [Cancer Res 2008;68(15):6043–8]

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