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Priority Reports

Targeting of the Bmi-1 Oncogene/Stem Cell Renewal Factor by MicroRNA-128 Inhibits Glioma Proliferation and Self-Renewal

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Key Words: glioblastoma • microRNA • stem cell

MicroRNAs (miR) show characteristic expression signatures in various cancers and can profoundly affect cancer cell behavior. We carried out miR expression profiling of human glioblastoma specimens versus adjacent brain devoid of tumor. This revealed several significant alterations,

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including a pronounced reduction of miR-128 in tumor samples. miR-128 expression significantly reduced glioma cell proliferation *in vitro* and glioma xenograft growth *in vivo*. miR-128 caused a striking decrease in expression of the Bmi-1 oncogene, by direct regulation of the Bmi-1 mRNA 3'-untranslated region, through a single miR-128 binding site. In a panel of patient glioblastoma specimens, Bmi-1 expression was significantly up-regulated and miR-128 was down-regulated compared with normal brain. Bmi-1 functions in epigenetic silencing of certain genes through epigenetic chromatin modification. We found that miR-128 expression caused a decrease in histone methylation (H3K27me³) and Akt phosphorylation, and up-regulation of p21^{CIP1} levels, consistent with Bmi-1 down-regulation. Bmi-1 has also been shown to promote stem cell self-renewal; therefore, we investigated the effects of miR-128 overexpression in human glioma neurosphere cultures, possessing features of glioma "stem-like" cells. This showed that miR-128 specifically blocked glioma self-renewal consistent with Bmi-1 down-regulation. This is the first example of specific regulation by a miR of a neural stem cell self-renewal factor, implicating miRs that may normally regulate brain development as important biological and therapeutic targets against the "stem cell-like" characteristics of glioma. [Cancer Res 2008;68(22):9125–30]

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