BMI1 sustains human glioblastoma multiforme stem cell renewal.

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Glioblastoma multiforme (GBM) is one of the most common and aggressive types of brain tumors. In GBM, a subpopulation of CD133-positive cancer initiating cells displays stem cell characteristics. The Polycomb group (PcG) and oncogene BMI1 is part of the Polycomb repressive complex 1 (PRC1) that regulates gene expression by modifying chromatin organization. Here we show that BMI1 is expressed in human GBM tumors and highly enriched in CD133-positive cells. Stable BMI1 knockdown using short hairpin RNA-expressing lentiviruses resulted in inhibition of clonogenic potential in vitro and of brain tumor formation in vivo. Cell biology studies support the notion that BMI1 prevents CD133-positive cell apoptosis and/or differentiation into neurons and astrocytes, depending on the cellular context. Gene expression analyses suggest that BMI1 represses alternate tumor suppressor pathways that attempt to compensate for INK4A/ARF/P53 deletion and PI(3) K/AKT hyperactivity. Inhibition of EZH2, the main component of the PRC2, also impaired GBM tumor growth. Our results reveal that PcG proteins are involved in GBM tumor growth and required to sustain cancer initiating stem cell renewal.

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