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## Article

### Epigenetic-Mediated Dysfunction of the Bone Morphogenetic Protein Pathway Inhibits Differentiation of Glioblastoma-Initiating Cells

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#### Summary

Despite similarities between tumor-initiating cells with stem-like properties (TICs) and normal neural stem cells, we hypothesized that there may be differences in their differentiation potentials. We now demonstrate that both bone morphogenetic protein (BMP)-mediated and ciliary neurotrophic factor (CNTF)-mediated Jak/STAT-dependent astroglial differentiation is impaired due to EZH2-dependent epigenetic silencing of BMP receptor 1B (*BMPR1B*) in a subset of glioblastoma TICs. Forced expression of *BMPR1B* either by transgene expression or demethylation of the promoter restores their differentiation capabilities and induces loss of their tumorigenicity. We propose that deregulation of the BMP developmental pathway in a subset of glioblastoma TICs contributes to their tumorigenicity both by desensitizing TICs to normal differentiation cues and by converting otherwise cyostatic signals to proliferative signals.

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