# BMPing Off Glioma Stem Cells

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DOI 10.1016/j.ccr.2007.12.018

**Brain tumor stem cells (BTSC) bear some similarities to neural stem cells (NSC). Bone morphogenetic proteins (BMPs) have a proproliferative effect on early embryonic NSC, and a prodifferentiative effect on postnatal NSC. In this issue of *Cancer Cell*, Lee et al. demonstrate that BMPs have differing effects on different BTSC lines, either promoting or inhibiting an astrocytic-like differentiation program. This latter effect is the result of epigenetic silencing of the *BMP receptor 1B* (*BMPR1B*). These findings document the importance of the BMP signaling system in BTSC as well as that of taking heterogeneity into account when studying BTSC as potential targets for therapy.**

Glioblastoma multiforme (GBM) is the most common brain tumor and one of the most highly lethal disorders with a median survival of 14.6 months (Stupp et al., 2005). The recent discovery of neural stem cell-like tumor cells, termed "brain tumor stem cells (BTSC)," a kind of cancer stem cell, in GBM has created a paradigm shift in brain tumor research. The BTSC theory dictates that tumors arise from a single, self-renewing cell type, which then gives rise to the rest of the tumor, including a variety of more differentiated cell types. Like neural stem cells, BTSC have the capacity for self-renewal and multipotent differentiation into cells expressing phenotypic markers of both neurons and glia (Ignatova et al., 2002; Hemmati et al., 2003; Singh et al., 2003). These cells are competent to serve as tumor initiating cells (TIC) in that they can form new brain tumors when implanted at low densities into immunodeficient mouse brain (Galli et al., 2004; Singh et al., 2004). The cancer stem cell theory, in general and as specifically applied to brain tumors, dictates that any therapy that fails to eradicate cancer stem cells can result in recurrence or regrowth of the residual tumor stem cells, resulting in subsequent failure of therapy. However, recent studies have suggested that BTSC are resistant to the currently utilized adjuvant therapies for GBM—radiation and temozolomide (Bao et al., 2006; Clement et al., 2007). Thus, new therapies that target BTSC are urgently needed.

One strategy to approach BTSC-specific therapy is to take advantage of current knowledge of neural stem and progenitor cell biology. Several studies have demonstrated numerous similarities between BTSC and the neural stem and progenitor cells that have been under intense scrutiny for the past 15 years, due to their potential to contribute to neural repair. Microarray and other gene expression analyses suggest that these phenotypic similarities are produced through the utilization of

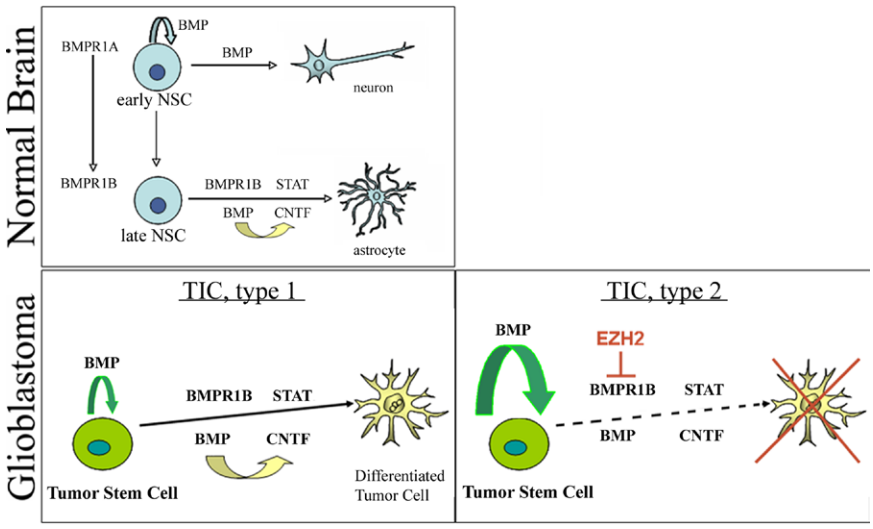


**Figure 1. BMP Effects on Normal Neural Stem Cells and Brain Tumor Stem Cells**
BMP effects on normal neural stem cells (top) and brain tumor stem cells (tumor initiating cells; bottom). In early neural stem cells, BMPs promote both neuronal differentiation and neural stem cell self-renewal. In later neural stem cells, the expression of BMPR1B allows the cells to respond to BMPs by differentiating into astrocytes. This differentiation response is mediated by activation of STAT, which can be induced by CNTF or LIF. In one type of brain tumor stem cell, referred to here as in the article as tumor initiating cells (TIC), BMPs promote astrocyte-like differentiation and inhibit proliferation via BMPR1B, which is also dependent on STAT signaling. In another type of TIC (type 2), BMPR1B expression is silenced by EZH2, thus preventing differentiation and promoting proliferation and tumorigenesis.

the same molecular pathways (Hemmati et al., 2003; Lee et al., 2006; Phillips et al., 2006). Thus, one might propose that factors that inhibit proliferation of neural stem and progenitor cells will also inhibit proliferation of BTSC.

Bone morphogenetic proteins (BMPs) are a family of cytokines with a complex set of effects on neural stem and progenitor cells. In neural stem cells derived from early embryons, BMPs appear to promote both proliferation as well as neuronal differentiation. In contrast, neural stem cells derived from older animals undergo astrocytic differentiation in response to BMPs (Panchision and McKay, 2002). This change in response patterns is mediated, at least in part in the acquisition of new signaling pathways by the older stem cells. Early neural stem cells express BMPR1A and have a limited response to ciliary neurotrophic factor (CNTF). On the other hand, older stem cells express BMPR1B, which then allows them to acquire responsiveness to CNTF-induced activation of STAT 3, which then promotes astrocytic differentiation.

The prodifferentiative role of BMPs in neural stem cells prompted investigators to study their roles in putative BTSC. Treatment of GBM-derived BTSC with BMPs—BMP4 having the strongest effect—results in an inhibition of proliferation, induction of differentiation and, importantly, a reduction in their ability to form tumors in immunodeficient mice, that is, to serve as TIC (Piccirillo et al., 2006). Thus, these TICs behaved like "older" neural stem cells in their response to BMP. In this issue, Lee and colleagues (Lee et al., 2008) also found that, in some patient-derived samples, BMPs promoted apparent glial differentiation in BTSC (termed TIC in the manuscript and in Figure 1). However, in one line, BMPs failed to induce glial differentiation but, rather, supported proliferation and promoted tumorigenesis. In a series of elegant studies, the authors found that the reason for these findings was that the BTSC in this line failed to express *BMPR1B* and, thus, did not attain competence to respond to CNTF or other factors to induce STAT3-dependent glial differentiation. Thus, these cells, in some ways, respond like "early" neural stem cells. Further studies demonstrate that *BMPR1B* was epigenetically silenced by an EZH2-dependent mechanism. Further study of multiple GBMs demonstrated that a minority, but significant number (approximately 20%), of GBM tumor samples available to the authors had low levels of *BMP1RB* and that the majority of these (6 out of 7) had hypermethylation of the promoter, demonstrating that the phenomenon described for the intensively studied cell line is not an isolated one. Of course, it will be interesting to determine the mechanisms by which those BTSC that have normal *BMP1RB* overcome the tendency to differentiate and maintain their self-renewal capacity.

The significance of the study lies not only in its elucidation of BMP function in BTSC, but also in the demonstration of the importance of tumor-to-tumor variation in BTSC. Although many studies have demonstrated commonalities among BTSC derived from different tumor types and different patients, it is clear that there can be fundamental differences in phenotypes of BTSC derived from different tumors, even when these tumors are of equivalent histological class and grade. These differences among BTSC could reflect both the differences between the oncogenic mutations expressed by the cells and their progeny and also differences in their cells of origin. Many people assume that because BTSC have similar properties to normal NSC, this implicates NSC as the cells of origin. However, there are multiple progenitor cell types within the CNS that have the inherent capacity for proliferation and even multilineage differentiation, and one might expect that the acquisition of oncogenic mutations that enhance their self-renewal capacity would result in differing tumor phenotypes. These differences among BTSC will ultimately need to be taken into account when developing treatments designed to target them for any individual patient.

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