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Hypoxia and HIF1alpha repress the differentiative effects of BMPs in high-grade glioma.

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Hypoxia commonly occurs in solid tumors of the central nervous system (CNS) and often interferes with therapies designed to stop their growth. We found that pediatric high-grade glioma (HGG)-derived precursors showed greater expansion under lower oxygen tension, typical of solid tumors, than normal CNS precursors. Hypoxia inhibited p53 activation and subsequent astroglial differentiation of HGG precursors. Surprisingly, although HGG precursors generated endogenous bone morphogenetic protein (BMP) signaling that promoted mitotic arrest under high oxygen tension, this signaling was actively repressed by hypoxia. An acute increase in oxygen tension led to Smad activation within 30 minutes, even in the absence of exogenous BMP treatment. Treatment with BMPs further promoted astroglial differentiation or death of HGG precursors under high oxygen tension, but this effect was inhibited under hypoxic conditions. Silencing of hypoxia-inducible factor 1alpha (HIF1alpha) led to Smad activation even under hypoxic conditions, indicating that HIF1alpha is required for BMP repression. Conversely, BMP activation at high oxygen tension led to reciprocal degradation of HIF1alpha; this BMP-induced degradation was inhibited in low oxygen. These results show a novel, mutually antagonistic interaction of hypoxia-response and neural differentiation signals in HGG proliferation, and suggest differences between normal and HGG precursors that may be exploited for pediatric brain cancer therapy.