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Hypoxia promotes expansion of the CD133-positive glioma stem cells through activation of HIF-1alpha.

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Hypoxia contributes to the progression of a variety of cancers by activating adaptive transcriptional programs that promote cell survival, motility and tumor angiogenesis. Although the importance of hypoxia and subsequent hypoxia-inducible factor-1alpha (HIF-1alpha) activation in tumor angiogenesis is well known, their role in the regulation of glioma-derived stem cells is unclear. In this study, we show that hypoxia (1% oxygen) promotes the self-renewal capacity of CD133-positive human glioma-derived cancer stem cells (CSCs). Propagation of the glioma-derived CSCs in a hypoxic environment also led to the expansion of cells bearing CXCR4 (CD184), CD44(low) and A2B5 surface markers. The enhanced self-renewal activity of the CD133-positive CSCs in hypoxia was preceded by upregulation of HIF-1alpha. Knockdown of HIF-1alpha abrogated the hypoxia-mediated CD133-positive CSC expansion. Inhibition of the phosphatidylinositol 3-kinase(PI3K)-Akt or ERK1/2 pathway reduced the hypoxia-driven CD133 expansion, suggesting that these signaling cascades may modulate the hypoxic response. Finally, CSCs propagated at hypoxia robustly retained the undifferentiated phenotype, whereas CSCs cultured at normoxia did not. These results suggest that response to hypoxia by CSCs involves the activation of HIF-1alpha to enhance the self-renewal activity of CD133-positive cells and to inhibit the induction of CSC differentiation. This study illustrates the importance of the tumor microenvironment in determining cellular behavior. *Oncogene* advance online publication, 31 August 2009; doi:10.1038/onc.2009.252.

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