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Neural stem cell tropism to glioma: critical role of tumor hypoxia.

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Abstract

Hypoxia is a critical aspect of the microenvironment in glioma and generally signifies unfavorable clinical outcome. Effective targeting of hypoxic areas in gliomas remains a significant therapeutic challenge. New therapeutic platforms using neural stem cells (NSC) for tumor-targeted drug delivery show promise in treatment of cancers that are refractory to traditional therapies. However, the molecular mechanisms of NSC targeting to hypoxic tumor areas are not well understood. Therefore, we investigated the role of hypoxia in directed migration of NSCs to glioma and identified the specific signaling molecules involved. Our data showed that hypoxia caused increased migration of human HB1.F3 NSCs to U251 human glioma-conditioned medium in vitro. In HB1.F3 NSCs, hypoxia led to up-regulation of CXCR4, urokinase-type plasminogen activator receptor (uPAR), vascular endothelial growth factor receptor 2 (VEGFR2), and c-Met receptors. Function-inhibiting antibodies to these receptors inhibited the migration of HB1.F3 cells to glioma-conditioned medium. Small interfering RNA knockdown of hypoxia-inducible factor-1alpha in glioma cells blocked the hypoxia-induced migration of NSCs, which was due to decreased expression of stromal cell-derived factor-1 (SDF-1), uPA, and VEGF in glioma cells. Our in vivo data provided direct evidence that NSCs preferentially distributed to hypoxic areas inside intracranial glioma xenografts, as detected by pimonidazole hypoxia probe, as well as to the tumor edge, and that both areas displayed high SDF-1 expression. These observations indicate that hypoxia is a key factor in determining NSC tropism to glioma and that SDF-1/CXCR4, uPA/uPAR, VEGF/VEGFR2, and hepatocyte growth factor/c-Met signaling pathways mediate increased NSC-to-glioma tropism under hypoxia. These results have significant implications for development of stem cell-mediated tumor-selective gene therapies.

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