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Knock down of HIF-1alpha in glioma cells reduces migration in vitro and invasion in vivo and impairs their ability to form tumor spheres.

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Abstract

ABSTRACT: BACKGROUND: Glioblastoma (GBM) is the most common and the most malignant primary intracranial human neoplasm. GBMs are characterized by the presence of extensive areas of necrosis and hypoxia. Hypoxia and its master regulator, hypoxia inducible factor 1 (HIF-1) play a key role in glioma invasion. RESULTS: To further elucidate the functional role of HIF-1alpha in glioma cell migration in vitro and in invasion in vivo, we used a shRNA approach to knock down HIF-1alpha expression complemented with genome-wide expression profiling, performed in both normoxic and hypoxic conditions. Our data show that knock down of HIF-1alpha in glioma cells significantly impairs their migration in vitro as well as their ability to invade into the brain parenchyma in vivo. Next, we assessed the role that HIF-1alpha plays in maintaining the characteristics of cancer stem cells (CSCs). By using the tumor sphere forming assay, we demonstrate that HIF-1alpha plays a role in the survival and self-renewal potential of CSCs. Finally, our expression profiling experiments in glioma cells provide a detailed insight into a broad range of specific biological pathways and processes downstream of HIF-1alpha and we discuss their role in the migratory and invasive properties as well as the stem cell biology of glioblastomas. CONCLUSIONS: Our data show that knock down of HIF-1alpha in human and murine glioma cells impairs their migration in vitro and their invasion in vivo. In addition, our data suggest that HIF-1alpha plays a role in the survival and self-renewal potential of CSCs and identify genes that might further elucidate the role of HIF-1alpha in tumor migration, invasion and stem cell biology.

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