



SIII 4. HOXA9 Promotes Glioblastoma Initiation, Aggressiveness and Resistance to Therapy

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Glioblastoma is the most common and malignant subtype of glioma, exhibiting remarkable resistance to treatment. Here we investigated the oncogenic potential of HOXA9 in gliomagenesis, the molecular and cellular mechanisms by which HOXA9 may render glioblastoma more aggressive, and how HOXA9 affects response to chemotherapy and prognosis. Expression microarrays were used to identify HOXA9 target genes. Stable glioblastoma cell lines with ectopic HOXA9 overexpression or shRNA-mediated knockdown of HOXA9 were established to evaluate the roles of HOXA9 in cell viability, death, invasion, and response to temozolomide. Subcutaneous and orthotopic intracranial xenograft models of glioblastoma were established to evaluate the oncogenic potential of HOXA9 *in vivo*, and its role in response to temozolomide and overall survival. Transcriptomic analyses identified novel HOXA9-target genes that have key roles in critical cancer processes, including cell proliferation, adhesion, DNA metabolism and repair, and stem cell maintenance. Functional assays with a variety of glioblastoma cells revealed that HOXA9 promotes cell viability, stemness, and invasion; conversely, HOXA9 displayed anti-apoptotic functions. Additionally, ectopic expression of HOXA9 promoted the malignant transformation of human immortalized astrocytes in an intracranial orthotopic mouse model of

glioblastoma, and caused tumor-associated death. HOXA9 also mediated resistance to temozolomide treatment both *in vitro* and *in vivo*. Mechanistically, BCL2 was identified as a novel HOXA9 target that may be therapeutically targeted. Indeed, the pharmacological inhibition of BCL2 with ABT-737 specifically reverted temozolomide resistance in HOXA9-positive cells. These data establish HOXA9 as a critical driver of glioma initiation, aggressiveness and resistance to therapy.

No conflict of interest.

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FUNDAÇÃO CALOUSTE GULBENKIAN
25-26 NOVEMBER 2014



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