Epigenetic silencing of Id4 identifies a glioblastoma subgroup with a better prognosis as a consequence of an inhibition of angiogenesis.

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Abstract

BACKGROUND: Inhibitors of DNA binding/differentiation (Id1 to Id4) are a family of helix-loop-helix transcription factors, which are highly expressed during embryogenesis and at lower levels in mature tissues. Id4 plays an important role in neuronal stem cell differentiation, and its deregulation has been implicated in glial neoplasia.

METHODS: The methylation status of Id4 was analyzed by methylation-specific polymerase chain reaction (PCR) in 62 glioblastoma (GBM) cases and in 20 normal brain tissues. Methylation status of Id4 was confirmed by sequencing after subcloning and messenger RNA (mRNA) and protein expression. We also evaluated the mRNA expression of MGP (matrix GLA protein), TGF-β1 (transforming growth factor beta 1), and VEGF (vascular endothelial growth factor) by real-time PCR analysis. Clinical and histological assessment of tumor angiogenesis was performed by evaluating the relative enhancing tumor ratio on magnetic resonance imaging and microvessel density on von Willebrand factor-stained sections, respectively.

RESULTS: The promoter of Id4 was methylated in 23 of 62 (37%) GBMs. In methylated GBMs, Id4 mRNA was significantly reduced, compared with unmethylated GBMs (P = .0002). A significant reduction of protein expression was detected in all hypermethylated cases. GBMs with methylated Id4 showed a significant reduction of MGP, TGF-β1, and VEGF mRNA expression and had significantly lower relative enhancing tumor ratio (P = .0108) and microvessel density (P = .0241) values with respect to unmethylated GBMs. Finally, Id4 methylation was significantly associated with a favorable clinical outcome (P = .0006).

CONCLUSIONS: These data suggest that methylation of Id4 may be involved in the pathogenesis of GBM and in the resistance of this neoplasm to conventional treatment throughout MGP-mediated neoangiogenesis. Cancer 2012. © 2012 American Cancer Society.

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PMID: 23132729 [PubMed - as supplied by publisher]

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