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An RNAi screen identifies TRRAP as a regulator of brain tumor-initiating cell differentiation.

Wurdak H, Zhu S, Romero A, Loriger M, Watson J, Chiang CY, Zhang J, Natu VS, Lairson LL, Walker JR, Trussell CM, Harsh GR, Vogel H, Felding-Habermann B, Orth AP, Miraglia LJ, Rines DR, Skirboll SL, Schultz PG.

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Glioblastoma multiforme (GBM) is a highly aggressive form of brain cancer associated with a very poor prognosis. Recently, the initiation and growth of GBM has been linked to brain tumor-initiating cells (BTICs), which are poorly differentiated and share features with neural stem cells (NSCs). Here we describe a kinome-wide RNA interference screen to identify factors that control the tumorigenicity of BTICs. We identified several genes whose silencing induces differentiation of BTICs derived from multiple GBM patients. In particular, knockdown of the adaptor protein TRRAP significantly increased differentiation of cultured BTICs, sensitized the cells to apoptotic stimuli, and negatively affected cell cycle progression. TRRAP knockdown also significantly suppressed tumor formation upon intracranial BTIC implantation into mice. Together, these findings support a critical role for TRRAP in maintaining a tumorigenic, stem cell-like state. Copyright 2010 Elsevier Inc. All rights reserved.

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