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Human neural stem cells target experimental intracranial medulloblastoma and deliver a therapeutic gene leading to tumor regression.

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Abstract

PURPOSE: Medulloblastoma, a malignant pediatric brain tumor, is incurable in about one third of patients despite multimodal treatments. In addition, current therapies can lead to long-term disabilities. Based on studies of the extensive tropism of neural stem cells (NSC) toward malignant gliomas and the secretion of growth factors common to glioma and medulloblastoma, we hypothesized that NSCs could target medulloblastoma and be used as a cellular therapeutic delivery system. **EXPERIMENTAL DESIGN:** The migratory ability of HB1.F3 cells (an immortalized, clonal human NSC line) to medulloblastoma was studied both in vitro and in vivo. As proof-of-concept, we used HB1.F3 cells engineered to secrete the prodrug activating enzyme cytosine deaminase. We investigated the potential of human NSCs to deliver a therapeutic gene and reduce tumor growth. **RESULTS:** The migratory capacity of HB1.F3 cells was confirmed by an in vitro migration assay, and corroborated in vivo by injecting chloromethylbenzamido-Dil-labeled HB1.F3 cells into the hemisphere contralateral to established medulloblastoma in nude mice. In vitro studies showed the therapeutic efficacy of HB1.F3-CD on Daoy cells in coculture experiments. In vitro therapeutic studies were conducted in which animals bearing intracranial medulloblastoma were injected ipsilaterally with HB1.F3-CD cells followed by systemic 5-fluorocytosine treatment. Histologic analyses showed that human NSCs migrate to the tumor bed and its boundary, resulting in a 76% reduction of tumor volume in the treatment group ($P < 0.01$). **CONCLUSION:** These studies show for the first time the potential of human NSCs as an effective delivery system to target and disseminate therapeutic agents to medulloblastoma.

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