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Mol Cancer Ther. 2010 Jul;9(7):2131-41. Epub 2010 Jun 29.

Identification of internalizing human single-chain antibodies targeting brain tumor sphere cells.

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Abstract

Glioblastoma multiforme (GBM) is the most common and aggressive form of primary brain tumor for which there is no curative treatment to date. Resistance to conventional therapies and tumor recurrence pose major challenges to treatment and management of this disease, and therefore new therapeutic strategies need to be developed. Previous studies by other investigators have shown that a subpopulation of GBM cells can grow as neurosphere-like cells when cultured in restrictive medium and exhibits enhanced tumor-initiating ability and resistance to therapy. We report here the identification of internalizing human single-chain antibodies (scFv) targeting GBM tumor sphere cells. We selected a large naive phage antibody display library on the glycosylation-dependent CD133 epitope-positive subpopulation of GBM cells grown as tumor spheres and identified internalizing scFvs that target tumor sphere cells broadly, as well as scFvs that target the CD133-positive subpopulation. These scFvs were found to be efficiently internalized by GBM tumor sphere cells. One scFv GC4 inhibited self-renewal of GBM tumor sphere cells *in vitro*. We have further developed a full-length human IgG1 based on this scFv, and found that it potently inhibits proliferation of GBM tumor sphere cells and GBM cells grown in regular nonselective medium. Taken together, these results show that internalizing human scFvs targeting brain tumor sphere cells can be readily identified from a phage antibody display library, which could be useful for further development of novel therapies that target subpopulations of GBM cells to combat recurrence and resistance to treatment. (c)2010 AACR.

PMID: 20587664 [PubMed - in process]

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