Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor. Despite multimodal therapy including surgical resection, radiation therapy and chemotherapy, GBM is uniformly lethal with a median survival of less than 15 months. In addition, currently available treatments can cause collateral, toxic effects to surrounding, non-transformed, healthy cells. By contrast, immunological targeting of tumor-specific mutations can allow for eradication neoplastic cells while leaving otherwise eloquent tissues intact.

T cells in particular play a major role in mounting effective antitumor immune responses, in some instances eradicating bulky, invasive neoplasms. Still, the widespread use of T cell-based immunotherapy faces a number of challenges. First, nonspecific activation of endogenous T cells, such as through global ligation with monoclonal antibodies, has resulted in disastrous autoimmune effects. In addition, immunological targeting of tumor-specific mutations can allow for eradication neoplastic cells while leaving otherwise eloquent tissues intact.

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Regulatory T cells (Tregs) play a central role in tumor escape from immunosurveillance. We report that a bispecific T-cell engager (BiTE) targeting a mutated form of the epidermal growth factor receptor, i.e., EGFRvIII, potently redirects Tregs to kill glioblastoma through the granzyme-perforin pathway.

Keywords: bispecific antibodies, central nervous system neoplasms, epidermal growth factor receptor, glioblastoma, granzymes, regulatory T cells

Regulatory T cells are redirected to kill glioblastoma by an EGFRvIII-targeted bispecific antibody

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Tregs are depleted in vitro, autologous T-cell proliferation and cytokine secretion return to normal levels. Furthermore, in vivo Treg depletion in tumor-bearing mice prolongs survival. Several investigators have attempted to translate these findings to enhance immune responses in human studies; however, strategies designed to deplete Tregs in the periphery do not efficiently eliminate the infiltrating, intratumoral population of Tregs, which may limit the therapeutic benefit of this approach. As a potential alternative, we have demonstrated that Tregs present in GBM may actually possess natural cytotoxic functions that can be reappropriated to directly kill tumors, and have provided data to support that such mechanisms can be manipulated advantageously through use of the BiTE therapeutic platform.

While these findings were obtained in the context of an EGFRvIII-specific BiTE, it is reasonable to believe that they can be extended to BiTEs targeting other tumor antigens. Further experiments are needed to elucidate the implications of our work with regard to the basic biology of Tregs, their cytotoxicity in the context of endogenous T cell receptor engagement, and the role of granzyme- and perforin-expressing Tregs that are naturally present in the tumor microenvironment.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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