Antibody-Based Immunotherapy for Malignant Glioma

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Conventional therapy for malignant glioma (MG) fails to specifically eliminate tumor cells, resulting in toxicity that limits therapeutic efficacy. In contrast, antibody-based immunotherapy uses the immune system to eliminate tumor cells with exquisite specificity. Increased understanding of the pathobiology of MG and the profound immunosuppression present among patients with MG has revealed several biologic targets amenable to antibody-based immunotherapy. Novel antibody engineering techniques allow for the production of fully human antibodies or antibody fragments with vastly reduced antigen-binding dissociation constants, increasing safety when used clinically as therapeutics. In this report, we summarize the use of antibody-based immunotherapy for MG. Approaches currently under investigation include the use of antibodies or antibody fragments to: (1) redirect immune effector cells to target tumor mutations, (2) inhibit immunosuppressive signals and thereby stimulate an immunological response against tumor cells, and (3) provide costimulatory signals to evoke immunologic targeting of tumor cells. These approaches demonstrate highly compelling safety and efficacy for the treatment of MG, providing a viable adjunct to current standard-of-care therapy for MG.
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MALIGNANT PRIMARY BRAIN TUMORS AND IMMUNOTHERAPY

Malignant primary brain tumors are the most frequent cause of cancer death in children,[1] are more common than Hodgkin lymphoma, and ovarian and testicular cancers, and are responsible for more deaths than malignant melanoma.[2] Despite aggressive, image-guided tumor resection,[3] high-dose external-beam radiotherapy[4] or brachytherapy,[5] optimized chemotherapy,[6] and recent advances in anti-angiogenic treatments,[7] patients with glioblastoma (GBM) live less than an average of 15 months from the time of diagnosis.[6,8]

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Standard-of-care therapies for malignant gliomas (MGs) fail to eliminate tumor cells specifically and as a result are limited by incapacitating damage to surrounding normal brain and systemic tissues.[9] In contrast, by virtue of exploiting the inherit specificity of the immune system, anti-cancer immunotherapy provides a promising, highly tumor-specific platform for safe and effective therapy. Pivotal approvals by the US Food and Drug Administration (FDA) for the immune-based cancer therapies sipuleucel-T and ipilimumab, which demonstrate significant survival benefits in patients with hormone-refractory prostate cancer and metastatic melanoma, respectively,[10,11] have further validated immunotherapy as a viable treatment modality for cancer.

ANTIBODIES AS AN IMMUNOTHERAPEUTIC MODALITY FOR INTRACEREBRAL MALIGNANCY

The exquisite epitope-binding-specificity imparted by monoclonal antibodies (mAbs) provides an ideal platform for precisely targeted immunotherapy. Intrinsic, high-affinity antigen recognition can be further enhanced with affinity maturation techniques, such as in vitro–directed evolution; this technique has produced antibody-derived single-chain variable fragments (scFvs) with dissociation kinetics

slower than the tightly bound streptavidin-biotin complex.[12] Further advances also have allowed for the production of fully human mAbs via phage display technology, transgenic mouse platforms and, more recently, mRNA and ribosome display,[13,14] drastically reducing the risk of immunogenicity against the drug and increasing clinical safety. Complications associated with murine antibodies previously used in the clinic, including cytokine release syndrome[15,16] and human anti-mouse antibody (HAMA) formation leading to rapid clearance from patients' serum,[17] unpredictable dose-response relationships,[16,18] and an acute, potentially severe influenza-like syndrome,[16,18–20] can be averted entirely.

While antibodies are present in the CNS in physiologic states,[21] glioma-induced changes render lesions particularly susceptible to antibody-based immunotherapy. Glioma tumor cells induce compositional changes in the basal lamina and astrocytic components of the neurovascular unit (NVU), disrupting the integrity of the blood-brain barrier (BBB). In addition to increasing tumor burden and heightening tumor invasion of the surrounding parenchyma,[22] this allows for enhanced penetrance of large soluble molecules, such as antibodies, from the vascular compartment. For the treatment of GBM, several studies have demonstrated that intravenously (IV) administered antibodies gain access to intracranial (IC) tumors and exert significant therapeutic benefit.[23–26] In murine GBM models, the anti-tenascin antibody (81C6) directed against a component of the tumor stroma showed significant localization and therapeutic activity following systemic administration,[23,24] and in clinical trials, IV administration of radiolabeled 81C6 showed selective tumor localization.[26] The antibody also accumulated in other tissues expressing high levels of tenascin, including the spleen, bone marrow and liver. As a further example, clinical evaluation of an antibody directed against the entirely tumor-specific mutation of the epidermal growth factor receptor (EGFRvIII), demonstrated higher levels of brain tumor–specific uptake following IV administration,[25] suggesting that in the absence of cross reactivity with peripherally located epitopes, such as that seen with tenascin, an antibody sink created by the exclusive expression of the target epitope within the CNS may result in enhanced antibody localization to the CNS.

TUMOR-SPECIFIC TARGETS AND EGFRvIII

The vast majority of the proteins found on the surface of tumor cells also are expressed on normal healthy tissue. While overexpression of specific surface antigens is characteristic of various tumors, most often these antigens are tumor-associated antigens also expressed on the surface of healthy cells. Targeting such tumor-associated antigens via immunotherapeutic methods holds great risk for autoimmunity and thereby undermines the specificity imparted by immunotherapeutic approaches. Tumor-specific antigens, however, occur as a result of mutations in somatic genes and, when targeted therapeutically, are far less likely to be associated with autoimmunity. Most tumor-specific antigens occur randomly due to the genetic instability inherent to human cancers[27] and as a consequence are patient-specific.

EGFRvIII, however, is a frequent and consistent tumor-specific mutation seen in approximately 31%–50% of patients with GBM[28–35] and in a broad array of other cancers.[33–41] Among patients with EGFRvIII-positive GBM, 37%–86% of tumor cells express the mutated receptor,[34] indicating that the mutation is translated with significant consistency. The mutation consists of an in-frame deletion of 801 base pairs in the extracellular portion of the wild-type receptor, generating a novel glycine residue at the fusion junction.[42,43] This produces a highly immunogenic, cell-surface, tumor-specific epitope.[44] Importantly, antibodies directed against EGFRvIII are entirely tumor-specific and do not cross react with the wild-type receptor located on untransformed, healthy cells.[44]

The mutated receptor plays a significant role in tumor pathobiology. EGFRvIII encodes for a constitutively active tyrosine kinase receptor[45,46] that enhances tumor cell growth[45,47,48] and invasion[49,50] while conferring radiation[51] and chemotherapeutic[52,53] resistance. Among patients with GBM, expression of EGFRvIII is an independent, negative prognostic indicator.[54] EGFRvIII also enhances the growth of neighboring EGFRvIII-negative tumor cells via cytokine-mediated paracrine signaling[55] and by transferring a functionally active oncogenic receptor to EGFRvIII-negative cells through the release of lipid-raft related microvesicles.[56] Recent research also has found that EGFRvIII is expressed in glioma stem cells (GSC),[57,58] an important consideration given the paradigm that tumor stem cells (TSCs) represent a subpopulation of cells that give rise to all differentiated tumor cells.[59] Altogether, the specificity, high frequency of surface expression and oncogenicity of the EGFRvIII mutation make it an ideal target for antibody-based immunotherapy.

BISPECIFIC ANTIBODY-REDIRECTED IMMUNOTHERAPY

MG lesions are characteristically heavily infiltrated with T cells,[60,61] and substantial evidence suggests that, if appropriately redirected, T cells, and in