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Immunotherapeutic Strategies for Brain Tumors

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1. Introduction

Cancer immunotherapy is the use of the immune system to reject cancers. The main premise is to harness the patient's immune system to attack the malignant tumor cells. This area of research has made tremendous progresses, and the United States Food and Drug Administration recently approved a vaccine for prostate cancers as the first approval for vaccines against non-viral cancers (Kantoff et al., 2010). However, when it comes to central nervous system (CNS) tumors, while early phase immunotherapy trials showed encouraging outcomes, the immunological microenvironment of the CNS and tumors arising in the CNS is still believed to be suboptimal for sufficient antitumor immune responses to mediate clinically-meaningful changes *in situ* (Okada, H. et al., 2009; Walker, P. R. et al., 2003). In this chapter, we first discuss recent advances in the CNS and CNS tumor immunology. We address factors that may promote immune escape of gliomas. We also review advances in passive and active immunotherapy strategies for glioma, with an emphasis on lessons learned from recent early phase clinical trials. We also discuss novel immunotherapy strategies that have been recently tested in non-CNS tumors with great potential for application to CNS tumors. We will finally discuss how each of these promising strategies can be combined to achieve clinical benefit for patients with CNS tumors.

2. Immunology of gliomas

2.1 Immunology of CNS

For many decades, the brain has been considered an immune-privileged site due to the presence of a blood brain barrier (BBB) and the lack of lymphatics (Ransohoff et al., 2003). More recent studies have revealed crucial components involved in the process of leukocyte migration towards the CNS and the mechanisms of neuroinflammatory reactions in the CNS (Ransohoff et al., 2003). This section will focus on three key issues of CNS immunology: 1) factors limiting inflammation in the CNS, 2) antigen-specific immune response in the CNS, and 3) immune cell trafficking towards the CNS. In-depth understanding of these aspects will allow us to gain a framework to improve current treatment strategies harnessing the immune system to treat brain tumors.

2.1.1 Factors limiting inflammation in the CNS

Cells composing the CNS are extremely sensitive to the toxic effects of exogenous substances. Therefore, the CNS and the neurovasculature system therein have evolved specialized mechanisms to control both molecular and cellular migration into and out of the CNS parenchyma and cerebral spinal fluid (CSF). Capillary endothelial cells in the CNS are termed the BBB due to their ability to restrict passive diffusion and maintain low pinocytotic activity, and neuroimmunologists synonymously use the term BBB to describe both the capillary and post capillary vessels, the latter of which is the site of T-cell migration into the brain (Ransohoff et al., 2003). This "barrier" results from the selectivity of the tight junctions (TJs) between endothelial cells in the CNS vessels that restrict the passage of large hydrophilic molecules (i.e. peptides and proteins) and cells (Abbott et al., 2006).

Many extracellular proteins have been studied as TJ proteins: primarily the occludin, claudin, and junctional adhesion molecule (JAM) families. Experimental characterization of each has shown that mice carrying a null mutation in the occludin gene develop normal TJs whereas claudins have been shown to be independently sufficient for TJ formation (Engelhardt, 2008), suggesting the importance of claudins in TJ formation and regulation. Additionally, intravenous injection of monoclonal antibodies blocking JAM into mice inhibits leukocyte accumulation in CSF and brain parenchyma presumably through blocking leukocyte transmigration at the BBB (Engelhardt, 2008).

2.1.2 Induction of Immune responses to CNS antigens

The classic paradigm of specific immune activation is achieved through antigen uptake by antigen-presenting cells (APCs), which migrate to the lymph nodes via draining lymphatics where APCs subsequently activate T-cells. In the systemic immune system, dendritic cells (DCs) are considered to be the most potent APCs. In the CNS, a variety of cell populations have been postulated as primary CNS APCs, including vascular endothelial cells, smooth muscle cells, astrocytes, perivascular macrophages, choroid plexus epithelial cells, neurons, and DCs (Dunn et al., 2007). Among them, microglia has been proposed to be the primary resident APCs in the CNS (Aloisi, 2001).

Presentation of CNS antigens can occur through multiple mechanisms (Walker, P. R. et al., 2003): 1) APC uptake antigen within the CNS and migrate to lymph nodes to present antigens; 2) antigen drains to lymph nodes where APCs take them up to present, and 3) cells that express the antigen directly drain to lymph nodes and present their own antigen (direct presentation as opposed to cross presentation by DCs). Indeed, DCs injected in brain tumors have been shown to migrate to the cervical lymph nodes (CLNs) (Dunn et al., 2007). In addition, autoantigens from brain lesions have been shown to drain to CLNs in both primate models of experimental allergic encephalomyelitis and human multiple sclerosis (de Vos et al., 2002). Concurrently, it has been shown that tumor-specific T-cells can be primed in CLNs in murine glioma models (Fujita et al., 2009; Kuwashima et al., 2005; Okada, N. et al., 2005).

2.1.3 Migration of immune cells towards the CNS

Lymphocytes traffic to the CNS through the following 4 steps: 1) tethering/rolling, 2) activation, 3) adhesion, and 4) transmigration (Engelhardt, 2008). Interactions between carbohydrates on leukocytes and adhesion molecules (usually selectins) on endothelial cells slow down the leukocytes. Chemokines (e.g. CXCL10) are released from a site of

inflammation and form a concentration gradient in endothelial membrane and attract responsible leukocytes such as activated T-cells (Fujita et al., 2009; Nishimura et al., 2006). At a reduced velocity, the leukocytes sense chemokines on the endothelial cells, become activated through G-protein signaling, and up-regulate integrins such as very late antigen 4 (VLA-4) (Sasaki et al., 2007; Sasaki et al., 2008a; Sasaki et al., 2008b; Sasaki et al., 2009). Lymphocyte function-associated molecules (LFAs) on lymphocytes allow for a stable interaction to their ligands vascular cell adhesion proteins (VCAMs) and inter-cellular adhesion molecules (ICAMs) on endothelial cells. Finally, with this tight interaction in place, the cells transmigrate into the parenchyma.

2.2 Immunosuppression by gliomas

Previously characterized immunological impairments in glioma patients have included low peripheral lymphocyte counts, reduced delayed-type hypersensitivity reactions to recall antigens, and impaired proliferating responses by peripheral blood mononuclear cells (PBMCs). Gliomas are known to achieve these by producing immunosuppressive molecules and inducing immunosuppressive leukocytes.

2.2.1 Immunosuppressive factors

Transforming growth factor β (TGF- β)

TGF- β is the most potent immunosuppressive cytokine; its biological effects are multiple and complex (Gorelik et al., 2002). They include the inhibition of 1) APC maturation 2) antigen presentation of APCs, 3) T-cell activation, and 4) their differentiation towards effector cells. Recent studies have shown that TGF- β is up-regulated in glioma cell clones that are resistant to the cytotoxic effects of allogeneic cytotoxic T-cells (CTLs), suggesting the significance of TGF- β in glioma immune escape mechanisms (Gomez et al., 2007; Ueda et al., 2009).

Interleukin 10 (IL-10)

IL-10 is also known to be a strong immunosuppressive cytokine (Moore et al., 2001). Like TGF- β , this cytokine has pleiotropic effects in immunoregulation and inflammation. It down-regulates the expression of Th1 cytokines, MHC class II antigens, and costimulatory molecules on APCs. The expression levels of IL-10 in glioma tissue correlate with glioma grade as well as a degree of brain invasiveness (Huettner et al., 1997; Nitta et al., 1994).

Prostaglandin E₂ (PGE₂)

PGE₂ is a product of arachadonic acid metabolism. It is produced at sites of inflammation or tissue damage where it exerts many effects including the enhancement of vascular permeability. As PGE₂ has profound modulatory effects on T-cell activation and gliomas synthesize PGE₂, it is associated with the suppressed T-cell function observed in patients with gliomas (Castelli et al., 1989). In addition, we recently demonstrated that PGE₂ production from murine gliomas induces accumulation of tumor-associated myeloid cells that promote growth of gliomas (Fujita et al., 2011).

CCL2; macrophage chemoattractive protein 1 (MCP-1)

CCL2, also known as MCP-1, is a chemokine secreted by a variety of glioma cell lines and expressed in glioblastoma multiforme (GBM) (Desbaillets et al., 1994; Takeshima et al., 1994). In addition to its angiogenic effects (Salcedo et al., 2000), it is associated with

recruitment of immunosuppressive leukocytes, such as tumor-associated macrophages and regulatory T cells (Fujita et al., 2010; Fujita et al., 2011; Huang et al., 2007; Jordan et al., 2008).

Fas receptor/ligand

The Fas receptor is a death receptor on the surface of cells that leads to apoptosis. Malignant gliomas express Fas ligand, which induces apoptotic cell death of adjacent immune cells infiltrating into tumors sites (Walker, P. R. et al., 1997). In addition, Fas receptor expressed on glioma cells induces proinflammatory and angiogenic mediators, which in turn protect and support tumors growth (Shinohara et al., 2000).

B7-homologue 1 (B7-H1); programmed death ligand-1 (PD-L1)

The B7 family consists of co-stimulatory molecules that positively and negatively regulate immune responses. Among them, B7-H1, also known as PD-L1, exerts immunosuppressive functions when interacting with its receptor PD-1 (Chen, 2004). Glioma cells express B7-H1, which subsequently inhibits T-cell functions by decreasing cytokine production levels (IFN- γ , IL-2, and IL-10) and expression levels of the T-cell activation marker CD69 (Wintterle et al., 2003). Glioma cells often exhibit mutations in a tumor-suppressor gene phosphatase and tensin homolog (PTEN), and loss of functions in PTEN also leads to up-regulation of B7-H1 (Parsa et al., 2007).

2.2.2 Immunosuppressive leukocytes

A large number of observations suggest that certain types of immune cells in the tumor microenvironment (TME) are not innocent bystanders at brain tumor sites, but they actively promote tumor development and progression. Inflammatory cells, primarily macrophage/microglia and regulatory T-cells, may affect these processes via their ability to express a large variety of factors, including immunoregulatory cytokines. These cytokines may be secreted not only by inflammatory cells, but also by the tumor cells and stroma cells, together establishing a network of factors that significantly affects brain tumor.

Macrophages/microglia

In the CNS, macrophage/microglial cells constitute the first line of cellular defense against a variety of stressors, participating in the regulation of innate and adaptive immune responses (Graeber et al., 2002). Resident microglia are CD11b⁺/CD45^{dim} whereas macrophages are CD11b⁺/CD45^{high}. Intratumoral macrophage/microglia density is higher than in normal brain and abundance of microglia correlates with the grade of malignancy (Badie et al., 2000).

In contrast, the defense functions of macrophage/microglia against glioma are compromised in the TME. Although these cells express Toll-like receptors (TLRs), critical components for APCs to mediate innate immune responses and activate adaptive immune responses, those in the TME are unable to activate T-cells properly (Hussain et al., 2006). Consistently, macrophages/microglia release many factors, including extracellular matrix proteases (MMPs) and cytokines, which may directly or indirectly influence tumor migration/invasiveness and proliferation (Watters et al., 2005). In addition, glioma cell migration is stimulated by the presence of macrophage/microglia (Bettinger et al., 2002). Taken together, macrophages/microglia in gliomas promote the invasive phenotype of these tumors.

Regulatory T-cells (Treg)

The suppressive activity of Tregs has been implicated as an important factor limiting immune-mediated destruction of tumor cells. The presence of CD4⁺FoxP3⁺ Tregs correlates

with impairment of T-cell proliferation in peripheral blood specimens in GBM patients (Fecci et al., 2006). Moreover, tumor infiltration by Tregs correlates with tumor grade and prognosis (Heimberger et al., 2008).

CD4⁺FoxP3⁺ Tregs in gliomas have been shown to express CD25, CTLA-4, GITR, and CXCR4 at high levels (Grauer et al., 2007). Intratumoral accumulation and activation of CD4⁺FoxP3⁺ Treg act as a dominant immune escape mechanism of gliomas and underline the importance of controlling tumor-infiltrating Treg in glioma immunotherapy.

3. Immunotherapy for gliomas

In this section, we will first discuss molecular targets for gliomas. Then, we will discuss two modalities: adoptive T-cell therapy (passive immunotherapy) and glioma vaccine (active immunotherapy).

3.1 Target molecules for gliomas

It is essential to know about potent target molecules for glioma immunotherapy. The following section will discuss selected human glioma-associated antigen (GAA)-derived epitopes that appear to be promising based on relatively restricted expression (compared with the normal brain) as well as well-characterized immunogenicity.

IL-13R α 2

IL-13R α 2 is a membrane glycoprotein that is overexpressed by >80% of malignant gliomas but is not expressed in normal brain tissues or other normal organs except for testes (Debinski et al., 1999). Therefore, IL-13R α 2 has attracted significant attention as a target for glioma therapy (Kahlon et al., 2004). We recently found that an analogue peptide of natural IL-13R α 2₃₄₅₋₃₅₃, in which the first and ninth amino-acid residues tryptophan and isoleucine have been replaced by valine and alanine, respectively, can elicit a greater CTL response against HLA-A2⁺ IL-13R α 2⁺ glioma cells compared with the natural peptide (IL-13R α 2_{345-353:1A9V}) (Eguchi et al., 2006).

EphA2

EphA2 is a tyrosine kinase receptor that plays a role in carcinogenesis (Dodelet et al., 2000). We have reported that EphA2₈₈₃₋₈₉₁ is expressed on gliomas and able to elicit an HLA-A2-restricted CTL response against glioma cell lines (Hatano et al., 2005). Furthermore, EphA2 mRNA overexpression was found to correlate inversely with survival in a panel of 21 GBMs (Liu et al., 2006). These findings support the idea that targeting of EphA2 by immunotherapy may provide a major impact in controlling tumor growth and prolonging patients' survival.

Survivin

Survivin is an apoptosis inhibitor protein overexpressed in most human cancers including gliomas (Blanc-Brude et al., 2002; Uematsu et al., 2005). Therefore, induction of immune response against Survivin appears to be an attractive strategy. Of interest, high level expression of Survivin was correlated with poor prognosis in patients with grade II or III astrocytomas (Uematsu et al., 2005).

Wilm's tumor 1 (WT1)

WT1 is a transcription factor oncogene that is overexpressed in various types of leukemia and solid tumor cells (Oka et al., 2002). Inhibition of WT1 in leukemic cell lines led to

decrease in proliferation and increase in apoptosis of tumor cells (Glienke et al., 2007). Human gliomas also express WT1 at high levels (Izumoto et al., 2008; Rushing et al., 2010; Schittenhelm et al., 2008). These findings imply that elimination of tumor cells that overexpress WT1 may allow efficient control against glioma growth.

Sry-related high mobility group box (SOX)

SOX is a family of transcriptional cofactors implicated in the control of diverse developmental processes and exhibit highly dynamic expression patterns during development of diverse tissues and cell types, especially during embryogenesis (Wegner, 1999). Indeed, SOX2 (Gangemi et al., 2009), SOX5 (Ueda et al., 2007), SOX6 (Ueda et al., 2004), and SOX11 (Schmitz et al., 2007) are highly expressed in glioma cell lines and a majority of glioma tissues. Their preferential expression in glioma and immunogenicity indicate that SOX proteins are attractive targets for immunotherapy.

Type III variant of the EGFR mutation (EGFRvIII)

EGFRvIII is present in 30-50% of patients with GBM. Despite the limited frequency in gliomas, EGFRvIII and IL-13R α 2 are expressed most restrictedly in primary glioma tissues compared with normal tissues (Saikali et al., 2007). Therefore, this antigen also appears to be an attractive target for glioma immunotherapy.

Cytomegalovirus (CMV)

Recent reports have demonstrated the presence of the cytomegalovirus (CMV) proteins as well as CMV mRNA in a majority of human GBMs (Barami, 2010; Cobbs et al., 2002; Lucas et al., 2010; Mitchell et al., 2008; Scheurer et al., 2008). Therefore, CMV in gliomas could serve as an immunotherapeutic target for glioma. In addition, the facilitation of an immune response against viral antigens contrasts with the difficulty of immunization against self antigens. It will be intriguing to introduce the CMV-derived epitope to multiepitope-based vaccine for glioma.

3.2 Adoptive T-cell therapy (ACT) for gliomas

ACT involves passive infusion or transfer of autologous CTLs specific for tumor antigens to the host. Although ACT are currently evaluated as experimental therapy for limited types of cancers (Gattinoni et al., 2006; Morgan et al., 2006), this strategy may hold promise as an attractive future immunotherapeutic intervention against gliomas. In particular, based on strong findings that CTLs have the capacity to migrate into brain parenchyma (Ransohoff et al., 2003), the approach has been vastly improved by the use of recent advances in several areas of human T-cell biology including *in vitro* human T-cell culture and *ex vivo* genetic manipulation. This section will focus on recent technological advances in ACT as well as a current and future ACT for glioma with an emphasis on recent perspectives from human studies.

3.2.1 Source of glioma-reactive CTLs

Peripheral Bloods

PBMCs from glioma patients can be expanded *in vitro* through multiple cycles of antigenic stimulation. Subsequently, cells with a monoclonal specificity to the particular GAA will be generated. Although few numbers of GAA-reactive CTLs might be obtained this method may be feasible as, this strategy has demonstrated favorable anti-tumor responses in cancer patients (Gattinoni et al., 2006).

Glioma tissues

Another important source of the GAA-specific CTLs is a glioma tissue itself. A tumor nodule contains tumor-reactive CTLs that can be first polyclonally expanded *ex vivo* in the presence of IL-2 and later selected for antigen specificity (Rosenberg, 2008). These CTLs derived from tumor nodules have been used for ACT in melanoma patients (Dreno et al., 2002; Dudley et al., 2005).

3.2.2 Manipulation of glioma-reactive CTLs *ex vivo*

Choice of T-cell subtypes

In general, an effector T-cell subset (T_E) is predominantly enriched during *ex vivo* expansion for ACT. T_E are generally considered to be terminally differentiated CTLs that have the highest cytotoxic capacity but lack appreciable proliferating capacity (Wherry et al., 2003). These cells would not be able to establish a long-term persisting population of tumor-specific CTLs. There is a significant association between clinically favorable responses and the persistence of *ex vivo* expanded melanoma-specific CTL clones after infusion (Robbins et al., 2004). Therefore, efforts have been made to generate long-term persisting CTLs. In contrast to the T_E subset, memory cells have enhanced proliferative potential and survival, and the potential to provide more robust and enduring protection against tumors (Perret et al., 2008). In particular, recent studies have highlighted the potential of central memory T-cells (T_{CM}) as a source of T_E for ACT (Wang et al., 2011; Yang et al., 2011). Yang *et al.* have shown that a large percentage of *in vitro* generated antitumor CTLs mimic a T_{CM} -like phenotype and function (Yang et al., 2011). In addition, Wang *et al.* have demonstrated that T_{CM} are less prone to apoptosis and able to establish a persistent reservoir of functional T-cells in mice (Wang et al., 2011). Furthermore, recent studies with human T-cell subsets have revealed that naïve $CD8^+$ cells were not only the most abundant subset but also the population most capable of *in vitro* expansion and T-cell receptor (TCR) transgene expression. Despite increased expansion, naïve-derived cells displayed minimal effector differentiation, a quality associated with greater efficacy after cell infusion (Hinrichs et al., 2011).

Cloning of high-avidity T-cell receptors (TCRs)

Since the majority of GAAs are poorly immunogenic to raise CTLs that possess TCRs with low avidity, a number of modifications have been made for ACT. One of the attempts is to systematically search tumor-specific $CD8^+$ T-cells for clone(s) with higher TCR avidity, clone TCR α and β genes, and exogenously induce the high-avidity TCR exogenously in bulk $CD8^+$ T-cells. Li *et al.* used phage display to search for a high-avidity TCR against an HLA-A0201-restricted epitope in a NY-ESO-1 antigen (Li et al., 2005). Moreover, ACT using high-avidity TCR transgenic T-cells have been shown to sustain in blood circulation at high levels; engineered cells were observed at 1 year after infusion in 2 of 15 patients who both demonstrated objective regression of metastatic melanoma lesions (Morgan et al., 2006). These data suggest the therapeutic potential of genetically engineered high-avidity TCR clones for glioma immunotherapy.

Establishment of chimeric antigen receptors (CARs)

An interesting alternative to expression of high-avidity TCRs on T-cells is to express a chimeric molecule that has antigen-binding domains of a monoclonal antibody fused with a signal transduction domain of CD3 (Gross et al., 1989), namely chimeric antigen receptors

(CAR). A significant advantage of CARs over TCRs is that the antigen recognition is not restricted by expression of certain MHC class I molecules. Recently, CARs have been used to treat a number of cancers (Cartellieri et al., 2010). CAR-based approaches are currently being developed for gliomas as well (Kahlon et al., 2004; Ohno et al., 2010).

3.2.3 Current attempts of ACT for gliomas

There have been a number of clinical trials for malignant gliomas using ACT (Table 1) (Vauleon et al., 2010). Among them, three Phase I trials (Holladay et al., 1996; Plautz et al., 1998; Wood et al., 2000) and two pilot studies (Plautz et al., 2000; Sloan et al., 2000) used CTLs obtained from lymph nodes or PBMCs after intradermal vaccination. Holladay *et al.* first conducted an ACT-based Phase I clinical trial and reported disease-free survival ≥ 8 months in 7 of 15 patients (Holladay et al., 1996). Later, Wood *et al.* demonstrated a correlation between clinical response and the predominance of CD8⁺ T-cells to CD4⁺ cells in the injected cells (Wood et al., 2000). In addition, DTH response to autologous tumors was shown to correlate with clinical response (Sloan et al., 2000; Wood et al., 2000). However, CTLs used in these studies were not specific for GAAs. Therefore, it is necessary to generate a library of human CTL clones against GAAs using advanced techniques described above. With such refinement of *ex vivo* T-cell manipulation, ACT may become a mainstream therapeutic intervention for malignant gliomas.

Study	Type of trials	Patients	Immune responses	Clinical responses
Holladay et al., 1996	Phase I	N = 15 recurrent HGG 12 GBM, 3 AA	DTH (15/15)	No PR or SD Median FPS: ≥ 8 mo
Plautz et al., 1998)	Phase I	N = 10 recurrent HGG 9 GBM, 1 AA		3 PR Median FPS: > 12 mo
Plautz et al., 2000	Pilot study	N = 9 recurrent HGG 6 GBM, 3 Gr3	DTH (9/9)	3 PR
Wood et al., 2000	Phase I	N = 12 newly diagnosed glioma 6 GBM, 2 Gr2, 4 Gr3	DTH (12/12)	4 PR, 2 SD <i>Correlation between clinical response and CD4/CD8 composition of infused cells</i>
Sloan et al., 2000	Pilot study	N = 19 recurrent HGG 16 GBM, 2 AA, 1 gliosarcoma	DTH (17/19)	1 CR, 7 PR, 9 SD Median OS : 12 mo <i>Correlation between survival and DTH response</i>

*Abbreviations used in this table. AA: anaplastic astrocytoma; CR: complete response; DTH: delayed-type hypersensitivity; GBM: glioblastoma; Gr2: WHO grade II glioma; Gr3: WHO grade III glioma; HGG: high-grade glioma; mo: month(s); OS: overall survival; PFS: progression-free survival; PR: partial response; SD: stable disease.

Table 1. ACT-based clinical trials for glioma

3.3 Glioma vaccines

In addition to the ACT strategy described above, we will discuss glioma vaccine strategies in this section. They include 1) whole glioma cell vaccines, 2) peptide-based vaccines targeting glioma-associated antigens, and 3) DC vaccines.

3.3.1 Whole glioma cell vaccines

Initial vaccination strategies for gliomas consisted of subcutaneous inoculations of irradiated, autologous (Wikstrand et al., 1980) or allogeneic (Zhang et al., 2007) glioma cells. This type of vaccine has the advantage of providing a panel of multiple potential GAAs that are naturally expressed by glioma cells. Especially, autologous glioma cells should allow immunizations against the most relevant GAAs expressed in the patient's tumor (i.e. tailored medicine). Potential downsides of this approach, however, include: 1) cumbersome procedures and quality control (QC)/quality assurance (QA) issues associated with large scale cultures of autologous glioma cells and 2) theoretical risks of autoimmune encephalomyelitis (Wikstrand et al., 1980). Nevertheless, this type of vaccine strategy has been carefully examined (Table 2). Schneider *et al.* (Schneider et al., 2001) and Steiner *et al.* (Steiner et al., 2004) reported pilot clinical trials using autologous glioma cells modified

Study	Type of trials	Patients	Tumor cell modification	Immune responses	Clinical responses
Schneider et al., 2001	Pilot study	N =11 newly diagnosed GBM	infected with NDV, inactivated with cisplatin	DTH (11/11) T cell infiltrate (4/4)	No survival benefit
Andrews et al., 2001	Pilot study	N =12 8 GBM, 4 AA	IGF-RA/AS ODN	T cell infiltrate (4/9)	2 CR, 4 PR, 2 SD
Steiner et al., 2004	Pilot study	N =23 GBM	infected with NDV	DTH (15/15) ELISPOT (3/3) T cell infiltrate (6/7)	1 CR Median OS: 100 wks
Parney et al., 2006	Pilot study	N =6 3 recurrent GBM 3 melanoma	transduced with B7-2 and GM-CSF	No CTL activity	Longer PFS (3/6 GBM)
Ishikawa et al., 2007	Pilot study	N =12 8 newly diagnosed GBM, 4 recurrent GBM	formalin-fixed	DTH (9/12)	1 CR, 1 PR, 2 MR Median OS: 10.7 mo
Clavreul et al., 2010	Phase I	N =5 recurrent HGG 4 GBM, 1 AOA	irradiated	DTH (2/5)	3 SD

*Abbreviations used in this table. AOA: anaplastic oligoastrocytoma; CTL: cytotoxic T-cells; ELISPOT: enzyme-linked immunosorbent spot; IGF-RA/AS ODN: insulin-like growth factor type I receptor antisense oligodeoxynucleotide; MR: minor response; NDV: Newcastle-Disease-Virus; wk: week(s).

Table 2. Autologous whole glioma cell vaccine trials.

with Newcastle-Disease-Virus (NDV), which is known to serve as an vaccine adjuvant and therefore to improve the efficacy of glioma vaccines. Recently, Ishikawa *et al.* reported a Phase I clinical trial using formalin-fixed glioma tissues as a source of antigens (Ishikawa *et al.*, 2007). The advantage of this strategy is that formalin fixation preserves the specific antigenicity of glioma cells. These studies reported no major adverse events.

3.3.2 Peptide-based vaccines targeting glioma-associated antigens

In vaccines using synthetic peptides for shared GAA-epitopes, advantages and disadvantages are distinct from those in whole glioma cell approaches. While synthetic GAA peptide-based vaccines may not adequately target antigens in each patient's tumor, these vaccines have less concern for autoimmunity and provide "off the shelf" feasibility. Indeed, a wide range of peptide-based vaccines have been clinically evaluated (Table 3). Yajima *et al.* reported a phase I study of peptide-based vaccinations in patients with recurrent malignant gliomas (Yajima *et al.*, 2005). In this study, prior to the first vaccine, each patient's PBMCs were evaluated *in vitro* for cellular and humoral responses against a panel of antigens, and peptides that induced positive response were used for vaccinations. The regimen was well tolerated and resulted in an 89-week median survival of treated patients. However, there is little evidence that the antigens used in this study are expressed in gliomas at high levels. More recently, as the extension of the approach, Terasaki *et al.* reported a Phase I trial using 14 HLA-A24-binding peptides (Terasaki *et al.*, 2011). They evaluated immune responses with dose escalation of peptides and defined 3 mg/peptide as the Phase II-recommended dose. Izumoto *et al.* reported a Phase II clinical trial using a single WT1 peptide (Izumoto *et al.*, 2008). In this study, they reported a median progression-free survival (PFS) of 20 weeks and a possible association between the WT1 expression levels and clinical responses. When single or oligo antigens are selected and targeted by vaccines, it also seems necessary to harness the concepts of epitope spreading to address the problems of tumor immune escape, while avoiding the augmentation of deleterious CNS autoimmune responses (Vanderlugt *et al.*, 2002). Sampson *et al.* recently reported a Phase II study targeting the EGFRvIII epitope in newly diagnosed GBM patients who received gross total resection (Sampson *et al.*, 2010). They reported a median PFS of 14.2 months and a median overall survival (OS) of 26.0 months. In addition, they identified that the development of specific antibody or delayed-type hypersensitivity responses to EGFRvIII significantly correlated with the OS.

Study	Type of trials	Patients	Peptide(s)	Immune responses	Clinical responses
Yajima <i>et al.</i> , 2005	Phase I	N = 25 17 GBM, 8 Gr3	multiple	DTH (11/21) CTL activity (14/21)	5 PR, 8 SD Median OS: 89 wks
Izumoto <i>et al.</i> , 2008	Phase II	N = 21 recurrent GBM	WT1	DTH (21/21)	2 PR, 10 SD Median PFS: 20 wks
Sampson <i>et al.</i> , 2010	Phase II	N = 18 newly diagnosed GBM	EGFRvIII	DTH (5/9) CTL activity (10/12)	Median PFS: 14.2 months Median OS: 26.0 mo
Terasaki <i>et al.</i> , 2011	Phase I	N = 12, recurrent GBM	multiple	CTL activity (8/12)	1 PR, 7 SD Median PFS: 2.3 mo Median OS: 18.9 mo

Table 3. Peptide-based vaccine trials for glioma.

3.3.3 DC vaccines

DCs are the most potent antigen-presenting cells, driving the activation of T-cells in response to invading microorganisms (Banchereau et al., 2000). The availability to culture DCs from human peripheral blood monocytes has generated significant interest in using DCs in novel cancer vaccination strategies (Banchereau et al., 2000).

To induce tumor-specific immune reaction via DCs, antigen elution from tumor cells has been performed (Table 4). Yu *et al.* reported a Phase I trial of vaccinations using DCs pulsed with peptides eluted from autologous glioma cells (Yu et al., 2001). Later, Liau *et al.* also reported a Phase I trial in patients with newly diagnosed GBM using DCs pulsed with acid-eluted glioma peptides (Liau et al., 2005). In this study, the authors reported the median OS of 23.4 months and that the benefit of the vaccine treatment was more evident in the subgroup of patients with slowly-progressing tumors and in those with tumors expressing low levels of TGF- β 2.

Study	Type of trials	Patients	Immune responses	Clinical responses
Yu et al., 2001	Phase I	N = 9 newly diagnosed HGG 7 GBM, 2 AA	CTL activity (4/7) T cell infiltrate (2/4)	Median OS: 455 d
Wheeler et al., 2004	Phase I/II	N = 25 newly diagnosed GBM	CTL activity (8/24)	3 PR
Liau et al., 2005	Phase I	N = 12 GBM 5 recurrent 7 newly diagnosed	CTL activity (6/12) T cell infiltrate (4/8)	1 PR Median OS: 23.4 mo

Table 4. DC-based vaccine trials using acid-eluted peptides.

However, pulsing DCs with eluted peptides requires a large culture of autologous glioma cells and time-consuming procedures, for which QC/QA is not always feasible. To overcome this issue, glioma cell lysate has been used to pulse DCs in a number of trials (Table 5). Yamanaka *et al.* reported a Phase I/II study using DC pulsed with glioma lysate. Patients received either DCs matured with OK-432 or DCs without OK-432-mediated maturation (Yamanaka et al., 2003; Yamanaka et al., 2005). GBM patients receiving mature DCs had longer survival than those receiving DCs without OK-432-mediated maturation. Furthermore, patients receiving both intratumoral and intradermal DC administrations demonstrated longer overall survival than those with intradermal administrations alone (Yamanaka et al., 2005). Wheeler *et al.* reported another Phase II clinical trial with lysate-pulsed DCs (Wheeler et al., 2008). IFN- γ production levels from post-vaccine PBMC correlated significantly with patients' survival and time to progression. Prins *et al.* recently reported a Phase I clinical trial in glioma patients using lysate-pulsed DCs (Prins et al., 2011). Interestingly, their gene expression profiling in the participants' GBM tissues demonstrated that the mesenchymal gene expression profile may represent a population of patients with favorable responses to their vaccines.

Study	Type of trials	Patients	Immune responses	Clinical responses
Yamanaka et al., 2003	Phase I/II	N = 10 7 GBM, 3 recurrent Gr3	DTH (3/6) ELISPOT (2/5) T cell infiltrate (2/2)	2 MR, 4 SD Median OS: > 200 wks
Yu et al., 2004	Phase I	N = 14 1 GBM, 1 AA, 9 recurrent GBM, 3 recurrent AA	CTL activity (4/9) T cell infiltrate (3/6)	Median OS: 133 wks
Rutkowski et al., 2004	Phase I	N = 12 recurrent HGG 11 GBM, 1 others	DTH (7/8)	2 CR, 1 PR, 1 SD Median OS: 10.5 mo
Yamanaka et al., 2005	Phase I/II	N = 24 recurrent HGG 18 GBM, 6 Gr3	DTH (8/17) ELISPOT (7/16)	1PR, 3MR, 10 SD Median OS: 480 d <i>Longer survival if DC maturation or IC injection</i>
Okada, H. et al., 2007	Phase I	N = 5 newly diagnosed GBM	No response	No response
Wheeler et al., 2008	Phase II	N = 34 GBM 23 recurrent 11 newly diagnosed	ELISPOT (17/34)	3 CR, 1 PR Median OS: 642 d <i>Correlation between survival and IFN-γ production</i>
De Vleeschouwer et al., 2004	Phase I/II	N = 56 recurrent GBM	DTH (11/ 23)	Median OS: 9.6 mo
Walker, D. G. et al., 2008	Phase I	N = 13 9 GBM, 4 AA	T cell infiltrate (3/3)	2 CR, 3 PR
Ardon et al., 2010	Phase I/II	N = 8 newly diagnosed GBM	DTH (2/5) ELISPOT (5/8)	Median OS: 24 mo
Prins et al., 2011	Phase I	N = 23 GBM 8 recurrent 15 newly diagnosed	increase in systemic TNF- α and IL-6	Median OS: 31.4 mo <i>Better immune response if mesenchymal gene expression presents</i>

Table 5. DC-based vaccine trials using autologous tumor cell lysates.

While these studies demonstrate early success of DC-based vaccines in glioma patients, based on our preclinical data demonstrating that type-1 CTLs are capable of mediating effective anti-CNS tumor immunity (Fujita et al., 2008; Nishimura et al., 2006), we recently completed a Phase I/II study of vaccines evaluating safety and immunological activities of vaccines using α -type-1-polarized DCs (α DC1) that are able to produce high levels of IL-12 and induce long-lived type-1 T-cell responses (Okada, H. et al., 2011). In this study, patients with recurrent malignant glioma received intra-lymphnodal injection of α DC1 loaded with synthetic peptides for GAA epitopes and administration of polyinosinic-polycytidylic acid

[poly(I:C)] stabilized by lysine and carboxymethylcellulose (poly-ICLC) in HLA-A2⁺ patients with recurrent malignant gliomas. GAAs for these peptides are EphA2, IL-13R- α 2, YKL-40, and gp100. The regimen was well-tolerated and induced positive immune responses against at least one of the vaccination-targeted GAAs in peripheral blood mononuclear cells in 58% of patients. Peripheral blood samples demonstrated significant up-regulation of type 1 cytokines and chemokines, including interferon- α and CXCL10. For at least 12 months, nine patients achieved progression-free status. One patient with recurrent GBM demonstrated a sustained complete response. IL-12 production levels by α DC1 positively correlated with time to progression. These data support safety, immunogenicity, and preliminary clinical activity of poly-ICLC-boosted α DC1-based vaccines and warrant further development of this approach. Although these Phase I/II studies demonstrate preliminary clinical efficacy, the ultimate judgment for clinical activity has to be made by rigorous evaluation in randomized studies.

Study	Type of trials	Patients	Antigen Source	Immune responses	Clinical responses
Kikuchi et al., 2001	Phase I	N =8 5 GBM, 2 AA, 1 AO	Fused tumor cells	ELISPOT (6/6)	1 MR, 6 SD
Caruso et al., 2004	Phase I	N =7 recurrent tumors 2 GBM, 1 AA, 4 others	tumor RNA	No PBMC respnse	1 PR, 4 SD
Kikuchi et al., 2004	Phase I	N =15 recurrent HGG 6 GBM, 7 AA, 2 OAA	Fused tumor cells	DTH (15/15) CTL activity (2/8)	4 PR, 2 SD, 1 MR
Sampson et al., 2009	Phase I	N =12 newly diagnosed GBM	EGFRvIII	DTH (5/9) CTL activity (10/12)	Median OS: 22.8 mo
Okada, H. et al., 2011	Phase I/II	N = 22 13 GBM, 5 AA, 3 AO, 1 AOA	EphA2, IL-13R- α 2, YKL-40, gp100	ELISPOT (10/22) increase in systemic Th1 cytokines	Median PFS: 4 mo (GBM) 13 mo (AG) <i>Correlation between survival and DC-derived IL-12 levels</i>

Table 6. Other DC-based vaccine trials for glioma.

4. Conclusion

We reviewed recent progress in the field of brain and brain tumor immunology. We also reported recent progress and current challenges in immunotherapeutic strategies for brain tumors. It is clear that the CNS and gliomas are equipped with numerous and layered immunosuppressive and immune escape mechanisms, perhaps including ones that we have not yet identified. These discoveries, however, allow us to develop strategies to overcome each of these mechanisms.

Remaining unique challenges against gliomas include relative difficulties in obtaining tumor tissues following immunotherapeutic treatments. Unlike other cancers, intracranial glioma tissues are not readily accessible following vaccine treatment. Designing neo-adjuvant settings with vaccines is not always feasible because recurrent malignant gliomas, for which surgical resection is clinically indicated, typically do not allow us to wait for weeks before surgery and often require treatment with high dose corticosteroids.

As reviewed in this article, the concept of immunotherapy has a diverse scope of strategies and target molecules. Extensive review of each field in this article has led us to identify the challenge for each strategy. Such challenges, however, may be overcome by appropriate combinations with other strategies. For example, ACT strategies may need to be combined with appropriate adjuvants and/or vaccinations to promote long lasting memory responses and anti-tumor immunosurveillance. However, when each of these agents is owned by separate industries with intellectual properties, such creative combinatorial strategies may not be implemented as efficiently as we would wish. Although several early phase clinical trials demonstrated promising therapeutic outcomes to date, clinical trials of immunotherapy for gliomas have not yet demonstrated objective proof of clinical efficacy in randomized studies. The eventual success of immunotherapies for brain tumors will be dependent upon not only an in-depth understanding of immunology behind the brain and brain tumors, but also the implementation of molecularly targeted trials that address multiple layers of challenges in brain tumors.

5. Acknowledgement

Financial Support: the National Institute of Health 2R01NS055140, 2P01NS40923, 1P01CA132714, P3CA047904.

6. References

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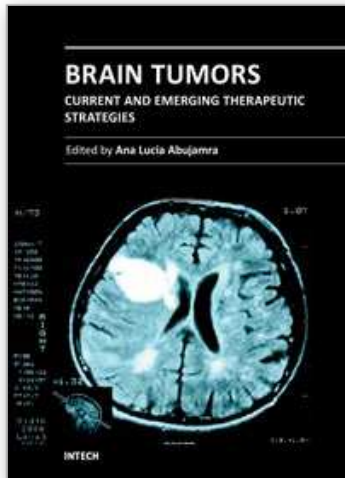
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Brain Tumors - Current and Emerging Therapeutic Strategies

Edited by Dr. Ana Lucia Abujamra

ISBN 978-953-307-588-4

Hard cover, 422 pages

Publisher InTech

Published online 23, August, 2011

Published in print edition August, 2011

Brain Tumors: Current and Emerging Therapeutic Strategies focuses on tumor models, the molecular mechanisms involved in the pathogenesis of this disease, and on the new diagnostic and treatment strategies utilized to stage and treat this malignancy. A special section on immunotherapy and gene therapy provides the most up-to-date information on the pre-clinical and clinical advances of this therapeutic venue. Each chapter in Brain Tumors: Current and Emerging Therapeutic Strategies is authored by international experts with extensive experience in the areas covered.

How to reference

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Mitsugu Fujita and Hideho Okada (2011). Immunotherapeutic Strategies for Brain Tumors, Brain Tumors - Current and Emerging Therapeutic Strategies, Dr. Ana Lucia Abujamra (Ed.), ISBN: 978-953-307-588-4, InTech, Available from: <http://www.intechopen.com/books/brain-tumors-current-and-emerging-therapeutic-strategies/immunotherapeutic-strategies-for-brain-tumors>

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