Neurosurg Rev (2011) 34:253–264
DOI 10.1007/s10143-011-0320-y

REVIEW

Cytokine networks in glioma

Kenichiro Iwami · Atsushi Natsume · Toshihiko Wakabayashi

Received: 10 September 2010 / Revised: 18 December 2010 / Accepted: 28 January 2011 / Published online: 9 June 2011

Abstract Glioma is the most frequently occurring brain tumor, but the prognosis of patients with gliomas remains poor despite advances in surgery, radiotherapy, and chemotherapy. Therefore, great efforts have been made to develop improved therapeutic strategies. Cytokines are a heterogeneous group of soluble small polypeptides or glycoproteins that exert pleiotropic and redundant effects that promote the growth, differentiation, and activation of normal cells. Cytokines have either pro- or anti-inflammatory activity and immunosuppressive activity, depending on the microenvironment surrounding the tumor. The microenvironment consists of heterogeneous tumor cells, immune cells, and extracellular matrix. Modulation of the microenvironment by the tumor is essential for its growth and progress. Cytokine production acts as a means of communication in the tumor microenvironment. In this article, we review the cross-talk between cytokines in the tumor microenvironment and the cytokine therapies that have been used till date for glioma treatment.

Keywords Glioma · Cancer immunology · Cytokine · Gene therapy

Introduction

Glioma is the most common and lethal primary brain tumor [67]. Current treatment regimens—including surgery followed by radiotherapy and chemotherapy—have improved the outcomes of patients with high-grade glioma (HGG) to some extent [109]. However, these improvements have had insufficient impact, and long-term control of the disease is rarely achieved. To manage this difficult-to-treat neoplasm, great efforts have been made to investigate the biological features of gliomas, including their cytokine networks. In this article, we review the cross-talk between cytokines in the tumor environment and the cytokine therapies that have been used till date for glioma treatment.

K. Iwami · A. Natsume · T. Wakabayashi (✉)
Department of Neurosurgery,
Nagoya University School of Medicine,
65 Tsurumai-cho, Showa-ku,
Nagoya 466-8550, Japan
e-mail: wakabat@med.nagoya-u.ac.jp

Immunology of the central nervous system

Since a long time, the brain has been referred to as an immune-privileged site and cannot augment the immune response because of lack of lymphatic structures, separation from systemic circulation by the blood–brain barrier, low expression of major histocompatibility complex molecules on most normal parenchymal cells, and a relatively high concentration of anti-inflammatory cytokines [17, 71]. These features can be considered as a protective mechanism from the overactive immune response that induces harmful brain edema [2, 12, 29, 61]. However, recent advances in the understanding of cytokine action has renewed the concept of immunology of the immune-privileged central nervous system (CNS) and interest in various immunotherapeutic approaches to neurological diseases [4, 29, 70, 95].

Glioma immunology

Even in the CNS, the immune system is of critical importance in tumor development and protects the host to a certain extent from tumor progression. Therefore, immunosuppression by gliomas is thought to contribute to tumor development,

progression, and resistance to treatment. Glioma cells down-regulate costimulatory molecules and modulate the tumor microenvironment in order to evade immune elimination [38, 41, 45, 46, 50, 99, 123]. A recent study revealed that the antiglioma response is not simply overwhelmed at advance stage of tumor growth but is counterbalanced by an inhibitory microenvironment from the outset [112]. Tumor-induced immunosuppression is likely to involve cross-talk among tumor cells, tumor-associated macrophages (TAMs), microglia, regulatory T cells (Tregs), and peripheral as well as tumor-infiltrating lymphocytes (TILs) [52, 53, 120]. The tumor microenvironment consists of a variable combination of tumor cells, immune cells, inflammatory cells, endothelial cells, and extracellular matrix. A variety of cytokines and other substances such as chemokines and growth factors are produced by different cells in the local tumor environment, resulting in complex cell–cell interaction and regulation of the differentiation, activation, functioning, and survival of multiple cell types. The interaction between cytokines and their receptors results in the formation of a comprehensive network at the tumor site that is primarily responsible for the overall progression of tumors, the spread of antitumor immune responses, and the induction of tumor rejection (Fig. 1).

Cytokines and cytokine therapies

Cytokines are a heterogeneous group of soluble small polypeptides or glycoproteins that exert pleiotropic and redundant effects that promote the growth, differentiation, and activation of normal cells [6]. Immune cells are the major source of cytokines, but many human cells are also capable of producing them, and importantly, cytokine production acts as a means of communication between both cells and tissue. Cytokines may be classified into the following categories: interleukin (IL) (1–15), growth factors, colony-stimulating factors, interferons (IFN) (α, β, and γ), tumor necrosis factor (TNF), and chemokines. These cytokines can have either pro- or anti-inflammatory activity and immunosuppressive activity, depending on the microenvironments. With respect to the glioma immunology and antiglioma therapy, the following cytokines should be understood.

Interleukin-4

Interleukin-4 (IL-4) is a glycoprotein with an approximate molecular mass of 15 kDa. It is secreted by several types of hematopoietic cells, including T cells, natural killer (NK) cells, basophils, eosinophils, and mast cells [76, 77, 96, 117, 130]. B cells, T cells, myeloid cells, monocytes, macrophages, mast cells, fibroblasts, endothelial cells, and some cancer cells express a high-affinity receptor that mediates the biological activity of IL-4 [7, 10, 91]. There are two types of IL-4 receptors (IL-4Rs): one consists of IL-4Rα and IL-2Rγ chains and is expressed on hematopoietic cells, whereas the other consists of IL-4Rα and IL-13Rα1 chains and is expressed on most leukocytes except T cells and on cells in the

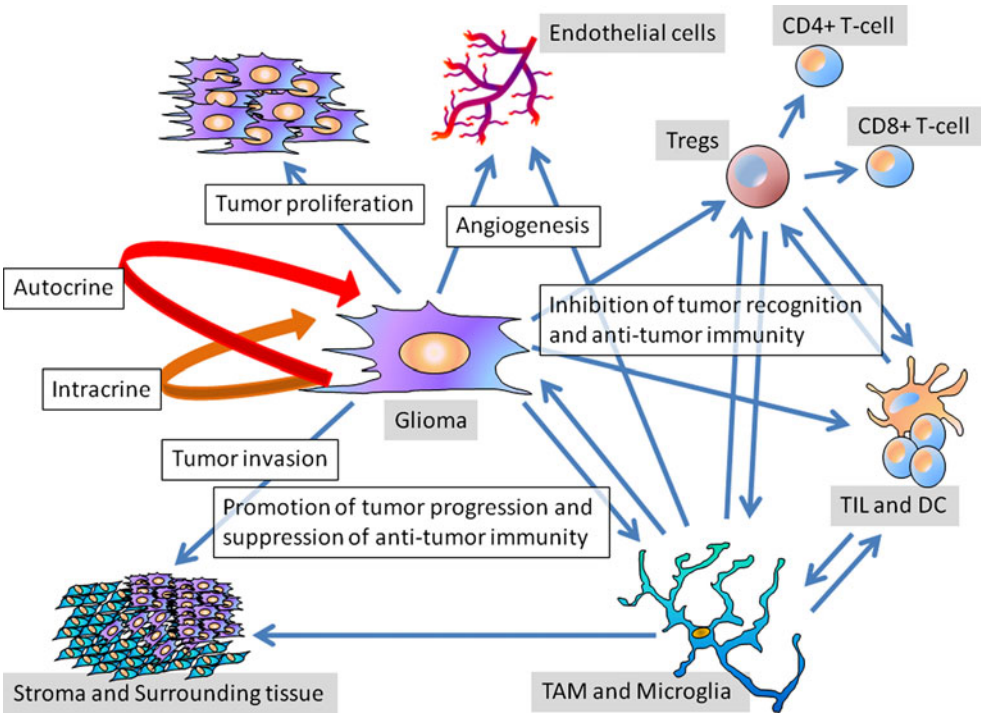

Fig. 1 Regulatory role of tumor-derived cytokines, chemokines, and growth factors in the tumor microenvironment. *TILs* tumor-infiltrating lymphocytes, *DCs* dendritic cells, *TAMs* tumor-associated macrophages, *Tregs* regulatory T cells

airway [27, 28]. IL-4 promotes the growth and differentiation of B cells, T cells, and mast cells and mediates regulatory effects to a great extent in macrophages. IL-4 stimulates the growth of both normal helper T cells and cytotoxic T cells (CTLs) including TILs and acts synergistically with IL-2 to enhance the proliferation of precursor CTLs (pCTLs) and induce their differentiation into active CTLs. Although IL-4 is generally regarded as an inducer of type 2 T cell responses, it is clearly shown that IL-4 has pleiotropic effects on immune cells of multiple lineages and that it plays an important role as an inducer of type 1 T cell immunity. In particular, IL-4 supports dendritic cell (DC) maturation and enhances IL-12p70 secretion from DCs [89].

A strategy for using IL-4 in glioma treatment is vaccinations with autologous glioma cells and *IL-4* gene-transfected fibroblasts [90]. Adult participants with recurrent glioblastoma multiforme (GBM) or anaplastic astrocytoma underwent gross total resection of the recurrent tumors, followed by two vaccinations with autologous fibroblasts retrovirally transduced with the IL-4 and thymidine kinase genes and mixed with irradiated autologous glioma cells. The patients who were vaccinated twice exhibited significant immunological and clinical responses.

Another promising strategy is the so-called immunotoxin therapy, which takes advantage of the fact that the IL-4R is abundantly present in malignant gliomas [121]. A chimeric recombinant fusion protein composed of circularly permuted IL-4 and a truncated form of *Pseudomonas* exotoxin (PE) has been evaluated as a potential therapeutic agent. In a phase I trial of IL-4-PE (NBI-3001) in patients with recurrent malignant gliomas, 31 patients were treated with intratumoral administration of IL-4R-PE via convection-enhanced delivery. Treatment-related adverse effects were limited, and no deaths were attributable to the treatment. Drug-related grade 3 and 4 toxicity was seen in 39% of the patients in all the dose groups and in 22% of the patients given the maximum tolerated dose. The median overall survival was 5.8 months in patients with recurrent GBM and 8.2 months in all patients.

These two strategies are thought to be safe and have acceptable toxicity profiles. However, further studies are needed to establish proof of IL-4 efficacy.

IL-10

IL-10 is a homodimeric polypeptide of 17 kDa, which was originally identified by Mosmann and colleagues [26, 74]. This cytokine is an anti-inflammatory cytokine and produced by many cells of both the innate and adoptive immune systems [25, 36, 75, 87, 88]. Some non-immune cells such as epithelial cells and tumor cells also produce IL-10 [75, 122]. The main biological function of IL-10 is exerted on DCs and macrophages, in which it is a potent inhibitor of antigen presentation and also inhibits the production of pro-inflammatory cytokines and mediators. IL-10 receptor belongs to the class II cytokine receptor family, thus IL-10 can inhibit the production of several cytokines such as IL-1β, IL-6, and TNF-α in various cells [75].

This immunosuppressive cytokine IL-10 is thought to play a crucial role in immunosuppression mediated by gliomas. Actually, increased IL-10 production has been reported in human gliomas [47]. Moreover, it is reported that glioma-generated factors induced the secretion of IL-10 by macrophages and microglia [126, 131].

It is suggested that all IL-10 bioactivity results in not only immune dysregulation but also enhancement of the function of B cells, NK cells, and $CD8^+$ T cells in infection models [11, 31, 100, 101]. Moreover, Benjamin et al. reported that IL-10-producing $CD4^+$ T cells mediated tumor rejection [106].

Several approaches are being investigated in pre-clinical studies to inhibit IL-10 activity, including antibodies to IL-10 or its receptor, antisense oligonucleotides, and small interference RNA. Further investigations are needed to better understand the role of IL-10 and to overcome the glioma-mediated immunosuppression.

IL-13

IL-13 is a cytokine derived from type 2 T helper cells and can bind to two receptor chains—IL-13Rα1 and IL-13Rα2. IL-13 has low affinity for the IL-13Rα1 chain and high affinity for the IL-4Rα chain. It forms a receptor complex with the IL-4Rα chain, which is involved in IL-13-induced signal transduction through either Janus kinase/signal transducer and activator of transcription (JAK-STAT) or phosphatidylinositol 3-kinase [127]. The IL-13Rα2 chain binds to IL-13 with high affinity and internalizes it after ligand binding, without the involvement of other chains.

IL-13R is found to be overexpressed in a majority of glioma cell lines and resected GBM specimens [18]. A chimeric fusion protein composed of human IL-13 and mutated PE has been developed and shown to affect the specific cytotoxicity of glioma cell lines [18, 78].

IL-13-PE is reported to be more active against glioma cell lines than are IL-4-targeted toxins in vitro [78]. In a phase I trial, 51 patients with GBM were administered IL-13-PE (cintredekin besudotox, also known as IL-13-PE38QQR) via convection-enhanced delivery [62]. A phase III study was conducted to compare the efficacy of IL-13-PE to that of Gliadel wafers in patients with malignant gliomas [78]. PFS was longer (17.7 versus 11.4 weeks) in patients treated with IL-13-PE than in patients treated with

Gliadel wafers, but no significant difference was observed in the median survival time between the two groups.

A more advanced strategy has been developed that involves conjugation of PE with a smaller single-chain variable fragment for producing anti-IL13R humanized antibodies [54]. Overall, IL-13-based toxins can potentially be used in adjuvant therapy for malignant gliomas, but their use requires further clinical studies.

Transforming growth factor-beta

Transforming growth factor-beta (TGF-β) is a multifunctional regulatory polypeptide belonging to a ligand superfamily that includes the TGF-βs, activins, and bone morphogenetic proteins (BMPs). TGF-β controls many aspects of cellular function, including proliferation, differentiation, migration, apoptosis, adhesion, angiogenesis, immune surveillance, and survival [1, 64, 68, 72, 94, 98]. Three mammalian TGF-β isoforms—TGF-β1, TGF-β2, and TGF-β3—have been identified. In normal adult tissues, TGF-β1 is by far the predominant isoform, and TGF-β2 and TGF-β3 expression is much lower than that of TGF-β1. The secreted TGF-β binds to TGF-β receptors (T-βRs) and initiates a signaling cascade via mediators of cytoplasmic signaling, which are called Smads, into the nucleus where the Smad complex regulates expression of various genes such as immunosuppressive-, angiogenesis-, and proliferation-related genes [20]. TGF-β activity is dependent on several factors, including cell type, growth conditions, and the presence of other polypeptide growth factors. Because of the dual role of TGF-β as a tumor suppressor and pro-oncogenic factor, the members of the TGF-β signaling pathway are considered to be predictive biomarkers of tumor progression as well as molecular targets for the prevention and treatment of cancer and metastasis [51].

In 1987, Wran and colleagues first identified TGF-β as T cell suppressor factor from human GBM [125]. The TGF-β2 isoform is specifically overexpressed in malignant gliomas. Increased TGF-β2 levels are associated with advanced disease stage and cause immunodeficiencies in patients with gliomas [55]. TGF-β2 not only inhibits lymphocyte proliferation but also has multiple effects on the immune system. These effects include the inhibition of immune cell activation, the blockade of antitumor activity, a shift of cytokine balance towards immunosuppression, and the inhibition of antigen presentation. Thus, targeted inhibition of TGF-β2 should have an antitumor effect and allow immune-mediated response. Several approaches to block TGF-β function are currently under study; for example, the use of monoclonal antibodies to TGF-β, recombinant fusion proteins containing the ectodomains of TGF-β receptor (TβR)II and TβRIII to prevent binding of TGF-β ligands, ATP competitive inhibitors at the ATP-binding site of TβRI kinase, and antisense oligonucleotides specific for *TGF-β2* [35, 40, 86, 105, 113, 114].

Trabedersen (AP-12009) is a synthetic antisense oligodeoxynucleotide designed to block TGF-β2 production [104]. In a randomized controlled phase IIb trial involving patients with brain tumors, the survival rates of patients for whom trabedersen was intratumorally administered were higher than those of patients receiving standard chemotherapy [115]. A randomized, controlled, dose-finding phase IIb study evaluated the efficacy and safety in 145 patients with recurrent or refractory high-grade glioma [5]. The patients were randomly assigned to receive trabedersen at dose of 10 or 80 μM or standard chemotherapy. Primary endpoint was 6-month tumor control rate. This study failed to meet the primary endpoint, but it could be due to the pseudoprogression with immune therapies. Prescribed anaplastic astrocytoma subgroup analysis showed significant benefit regarding the 14-month tumor control rate for 10 μM trabedersen. The 2-year survival rate had a trend for superior for 10 μM trabedersen. An international clinical phase III trial is currently recruiting patients with recurrent or refractory anaplastic astrocytoma with endpoints of 14-month progression rate and 2-year survival rate.

IL-2

IL-2 is a growth factor of the immune system, which includes helper T cells, CTLs, B cells, NK cells, and macrophages. IL-2 also enhances the production of other cytokines such as TNF, IL-1, and IFN-γ. Studies have shown that IL-2 enhances the mitogenesis of lymphocytes as well as the proliferation and clonal expansion of lymphokine-activated killer cells (LAKs), which are mainly NK cells induced into a hyperactive state and TILs. Initial efforts were mostly focused on the use of cytokines to increase the number of LAKs and TILs and then on the use of these cells to treat tumors such as renal cell carcinomas and melanomas [6, 12, 49, 116, 120]. In addition to its use in adoptive immunotherapy, IL-2 was used as a pharmacological agent to be directly administered into the patient's body; however, because of the serious adverse reactions such as hypotension, renal dysfunction, myocardial infarction, bowel perforation, seizures, and coma, clear clinical benefits were seen only in a limited number of patients.

The first clinical trial for IL-2 therapy in glioma patients was reported in 1986. Recombinant IL-2 or autologous LAK cells were directly injected into the tumor cavity for nine patients. In this phase I study, there were no signs of systemic toxicity or neurotoxicity after treatment [49]. In other trials, IL-2 was mainly administered into a cavity, and this was followed by tumor resection [37, 60, 116]. In one

trial, however, a combination of autologous tumor vaccination and systemic IL-2 administration was used [42], but even in this study, the systemic IL-2 dose was reduced from 8.8×10^6 to 3×10^6 U/day for the last seven patients because of the considerable discomfort caused by IL-2 therapy.

The efficacy of combination therapy with a suicide gene and the *IL-2* gene for treating recurrent GBM was recently investigated [16]. In this study, 12 patients received intratumoral injections of retroviral vector-producing cells, followed by intravenous ganciclovir. This treatment was well tolerated: two patients showed a partial response; four, a minor response; four, stable disease; and two, progressive disease. The 6- and 12-month progression-free survival (PFS) rates were 47% and 14%, respectively, and the 6- and 12-month overall survival rates were 58% and 25%, respectively. Although these studies did not reach conclusion regarding the efficacy of IL-2, it is thought that IL-2 has the potential to amplify the antiglioma immune response.

Granulocyte-macrophage colony-stimulating factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is secreted by various types of cells such as monocytes, endothelial cells, activated T cells, fibroblasts, mitogen-stimulated B cells, and lipopolysaccharide (LPS)-stimulated macrophages. GM-CSF binds to a high-affinity receptor composed of a GM-CSF-specific α chain and the conventional signal-transduction subunit, i.e., the β-subunit, which is also present in the receptors for IL-3 and IL-5. The activation of the GM-CSF receptor is known to stimulate three pathways: the JAK-STAT, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K) pathways. The GM-CSF receptor is expressed by $CD34^+$ progenitor cells, all myeloid lineages, and vascular endothelial cells. GM-CSF can promote myeloid differentiation and, in fact, it was first defined by its ability to generate both granulocyte and macrophage colonies from bone marrow precursor cells. However, GM-CSF also plays an important role in the host response to external stimuli, inflammation, and antitumor immune responses. These pivotal roles mainly derive from the ability of GM-CSF to affect the properties and functional status of immature and mature myeloid cells such as granulocytes, DCs, macrophages, and eosinophils [92].

GM-CSF has been widely used as an adjuvant in clinical trials involving vaccination with autologous tumor cells, peptides, and/or DCs in different human neoplasms; in these trials, GM-CSF was administered subcutaneously or intradermally—either as a product of gene-transduced tumor cells or as a recombinant protein—together with the vaccine. Autologous or allogeneic human tumor cells transduced with the GM-CSF gene have been tested as vaccines in many cancers, such as renal cancer, melanoma, prostate cancer, lung cancer, and pancreatic tumors. A pilot clinical trial of combined *B7-2* and *GM-CSF* immunogene therapy for GBMs and melanomas has been reported [93]. In this trial, patients with recurrent malignant gliomas were vaccinated with irradiated autologous tumor cells transduced with the genes encoding B7-2 and GM-CSF, using a retroviral vector. Although vaccine preparation was attempted using 116 samples of malignant glioma tissue, it was successful only in the case of five GBM samples. Minor toxicities were observed, and all patients have now died. Most patients showed evidence of an inflammatory response, but specific antitumor immunity was not observed. The GM-CSF protein is also widely used as an adjuvant at the site of vaccination to avoid the cumbersome procedure of gene transduction and to determine the appropriate dose of the cytokine for administration to other tumors. Nineteen patients with recurrent malignant glioma were vaccinated twice with irradiated autologous whole tumor cells, using GM-CSF as an adjuvant. The patients then underwent leukapheresis, followed by adoptive transfer of peripheral blood lymphocytes that were activated in vitro by using anti-CD3 antibody and IL-2. Of the 19 patients, 17 developed a delayed-type hypersensitivity (DTH) response to vaccination, which appeared to be directed against the autologous tumor. In eight patients, there was radiological evidence of a response, and in five, there was evidence of clinical improvement. The median survival time was 12 months (range, 6–28 months), and the presence of both, a DTH response and a radiological response, correlated with survival [108]. While GM-CSF immunotherapy has been promising in pre-clinical studies, further studies are required to bring these benefits to more patients.

IFN-α

The IFNs were originally discovered as agents that interfere with viral infection [48]. They are classified into types I and II according to receptor specificity and sequence homology. Type I IFNs are produced by many cells in response to viral infection and are principally concerned with targeting viral RNA translation into protein. Type I IFNs directly inhibit proliferation of tumor cells through various mechanisms including induction of apoptotic cell death [13, 69, 81, 111]. Their biological effects on DCs include maturation and promotion of antigen-presenting ability [19, 43, 63, 73]. It has also been reported that activation of DCs with IFN-α or -β leads to upregulation of TNF-α-related apoptosis-inducing ligand (TRAIL) expression, and to direct tumoricidal activity mediated by DCs via TRAIL [65, 102].

Although IFN-α has been used therapeutically for patients with malignant gliomas, varying efficacy has been reported [4, 8, 9, 21, 39, 79, 80, 97, 128].

There are two forms of recombinant IFN commercially available : α2a and α2b, which are thought to be equally effective. Recently, two phase II trials using temozolomide (TMZ) with either pegylated or non-pegylated IFN-α2b in patients with recurrent GBM were conducted [32]. Both studies with either pegylated or non-pegylated IFN-α2b showed improved efficacy when compared to historical controls. Even though the TMZ±pegylated IFN-α2b study met criteria for further study, IFN-α2b has the potential to be used as a promising adjunct to TMZ for GBM patients.

IFN-β

IFN-β is type I IFN and has pleiotropic biological effects and has been widely used either alone or in combination with other antitumor agents for treating malignant gliomas and melanomas [14]. IFN-β acts as a drug sensitizer during the treatment of malignant gliomas and enhances toxicity against various neoplasms when administered in combination with nitrosourea.

Combination therapy with IFN-β and nitrosourea has been used for treating gliomas in Japan [118]. Previously, we demonstrated that IFN-β markedly enhanced chemosensitivity to TMZ in an in vitro study of human glioma cells [84]; this finding suggests that one of the main mechanisms by which IFN-β enhances chemosensitivity is the downregulation of O^6-methylguanine methyltransferase (MGMT) transcription via *p53* induction. This effect was also observed in an experimental animal model [85]. The results of these two studies suggest that use of chemotherapy with IFN-β and TMZ together with radiation might improve the clinical outcome in patients with malignant gliomas to a greater extent than might the combined use of TMZ and radiation therapy.

In 2000, a clinical trial was conducted at Nagoya University, Japan, using cytokine gene therapy, wherein the *IFN-β* gene was delivered via cationic liposomes. This gene therapy system induced specific cytotoxic T cell immunity against mouse glioma and NK cells [82, 83]. On

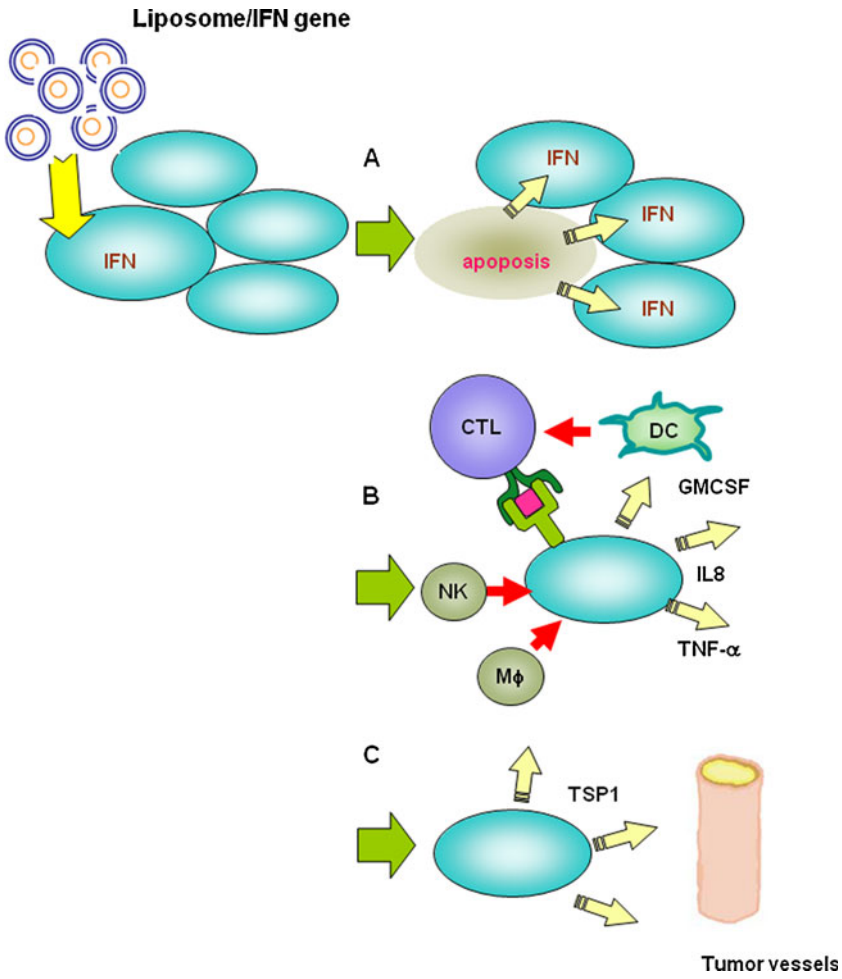

Fig. 2 Mechanisms of liposome-mediated IFN-β gene therapy. Histological and cDNA expression microarray analyses revealed significant induction of apoptosis (**a**), antitumor immunoresponse (**b**), and inhibition of neovascularization (**c**)

the basis of these results, a phase I clinical trial of *IFN-β* gene therapy was conducted in five patients with recurrent malignant gliomas [129]. This was a two-stage trial in which the initial treatment comprised tumor resection and injection of liposomes containing the human *IFN-β* gene into the margin of the resulting defect and delivery of subsequent injections via an implanted catheter. The clinical toxicity was found to be minimal. At 10 weeks after treatment initiation, two patients showed more than 50% reduction in tumor size while others had stable disease. The median survival time was longer in the treated subjects than in the matched historical controls from our institution. After the gene therapy, significant histological and gene expression changes related to immunoresponse, apoptosis, and neovascularization were observed [119] (Fig. 2). This study provided the foundation for a phase II trial of *IFN-β* gene therapy. Very recently, Chiocca et al. reported a phase I clinical trial (with a dose-escalation cohort) that involved stereotactic injection of an IFN-β-expressing adenoviral vector in 11 patients with malignant glioma. Direct injection of the vector into the tumor and the surrounding normal areas in the brain after surgical resection of the tumor was feasible. A reproducible increase in tumor cell apoptosis was observed after the treatment [15].

IFN-γ

IFN-γ is the sole type II IFN secreted by T cells and NK cells, which produces a variety of physiologic and cellular responses through transcriptional regulation [3]. IFN-γ affects the recognition of tumor by the immune system through the expression of major histocompatibility complex antigens on the cell surface and induces activation and differentiation of T cells, B cells, macrophages, NK cells, and antigen-presenting cells [34, 103]. IFN-γ has direct antitumoral activity and has been implicated as an anti-angiogenic factor [57–59, 107, 110]. IFN-γ has been shown to play a key role in inducing expression of death ligands on the surface of immune cells, including Fas ligand (FasL) and TRAIL. Although the human glioma cells vary in their susceptibility, FasL and TRAIL can induce apoptosis by binding to their death domain containing receptors [56]. It is important to also note that IFN-γ induces IL-6, which is related to treatment resistance in gliomas and is known as a negative prognostic factor in renal cell carcinoma [22, 44, 66].

The efficacy of intratumoral recombinant IFN-γ treatment in newly diagnosed GBM patients was investigated [24]. In this study, 32 patients were randomized to receive open cytoreduction plus external irradiation of 60 Gy with or without intratumoral IFN-γ. There were no differences in the tumor progression and the survival times between the IFN-γ treated and control groups.

Johannes et al. reported the maintenance treatment with IFN-γ for pediatric high-grade glioma [124]. After induction treatment with simultaneous radiation and chemotherapy, 40 patients were treated with IFN-γ and low-dose cyclophosphamide. There was mild toxicity in this approach, but no inspiring efficacy was reported.

The place of IFN-γ on clinical treatment is still being delineated at this time, but current pre-clinical studies suggest that IFN-γ has the potential to be used as a promising adjunct to other therapeutic products [23, 30, 33].

Future directions

The immunological response against tumors involves a critical balance between immune-activating and immune-suppressing mechanisms. Tumors contain immune cells and a network of pro- and anti-inflammatory cytokines collaborate in the development and progression of cancer. We believe that tumors may be more readily controlled via their microenvironments. Cytokine-based drugs and anticytokines are increasingly playing a crucial role in the treatment of malignant gliomas. Current research is aimed at developing new therapies, refining therapies that are already in use, and establishing the safest and most effective dosage levels. The latest development in the field of cytokines is the use of cytokine gene therapy rather than systemic administration of cytokines for the treatment of malignant gliomas. However, further studies are required to evaluate the effectiveness of these approaches.

References

1. Aigner L, Bogdahn U (2008) TGF-beta in neural stem cells and in tumors of the central nervous system. Cell Tissue Res 331:225–241
2. Barker CF, Billingham RE (1977) Immunologically privileged sites. Adv Immunol 25:1–54
3. Boehm U, Klamp T, Groot M, Howard JC (1997) Cellular responses to interferon-gamma. Annu Rev Immunol 15:749–795
4. Boethius J, Blomgren H, Collins VP, Greitz T, Strander H (1983) The effect of systemic human interferon-alpha administration to patients with glioblastoma multiforme. Acta Neurochir (Wien) 68:239–251
5. Bogdahn U, Hau P, Stockhammer G, Venkataramana NK, Mahapatra AK, Suri A, Balasubramaniam A, Nair S, Oliushine V, Parfenov V, Poverennova I, Zaaroor M, Jachimczak P, Ludwig S, Schmaus S, Heinrichs H, Schlingensiepen KH (2011) Targeted therapy for high-grade glioma with the TGF-{beta}2 inhibitor trabedersen: results of a randomized and controlled phase IIb study. Neuro Oncol 13:132–142
6. Borish LC, Steinke JW (2003) 2. Cytokines and chemokines. J Allergy Clin Immunol 111:S460–S475
7. Boulay JL, Paul WE (1992) The interleukin-4-related lymphokines and their binding to hematopoietin receptors. J Biol Chem 267:20525–20528

8. Brandes AA, Scelzi E, Zampieri P, Rigon A, Rotilio A, Amista P, Berti F, Fiorentino MV (1997) Phase II trial with BCNU plus alpha-interferon in patients with recurrent high-grade gliomas. Am J Clin Oncol 20:364–367
9. Buckner JC, Brown LD, Kugler JW, Cascino TL, Krook JE, Mailliard JA, Kardinal CG, Tschetter LK, O'Fallon JR, Scheithauer BW (1995) Phase II evaluation of recombinant interferon alpha and BCNU in recurrent glioma. J Neurosurg 82:430–435
10. Cabrillat H, Galizzi JP, Djossou O, Arai N, Yokota T, Arai K, Banchereau J (1987) High affinity binding of human interleukin 4 to cell lines. Biochem Biophys Res Commun 149:995–1001
11. Cai G, Kastelein RA, Hunter CA (1999) IL-10 enhances NK cell proliferation, cytotoxicity and production of IFN-gamma when combined with IL-18. Eur J Immunol 29:2658–2665
12. Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC (2006) CNS immune privilege: hiding in plain sight. Immunol Rev 213:48–65
13. Chawla-Sarkar M, Leaman DW, Borden EC (2001) Preferential induction of apoptosis by interferon (IFN)-beta compared with IFN-alpha2: correlation with TRAIL/Apo2L induction in melanoma cell lines. Clin Cancer Res 7:1821–1831
14. Chawla-Sarkar M, Lindner DJ, Liu YF, Williams BR, Sen GC, Silverman RH, Borden EC (2003) Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. Apoptosis 8:237–249
15. Chiocca EA, Smith KM, McKinney B, Palmer CA, Rosenfeld S, Lillehei K, Hamilton A, DeMasters BK, Judy K, Kirn D (2008) A phase I trial of Ad.hIFN-beta gene therapy for glioma. Mol Ther 16:618–626
16. Colombo F, Barzon L, Franchin E, Pacenti M, Pinna V, Danieli D, Zanusso M, Palu G (2005) Combined HSV-TK/IL-2 gene therapy in patients with recurrent glioblastoma multiforme: biological and clinical results. Cancer Gene Ther 12:835–848
17. Cserr HF, Knopf PM (1992) Cervical lymphatics, the blood–brain barrier and the immunoreactivity of the brain: a new view. Immunol Today 13:507–512
18. Debinski W, Obiri NI, Powers SK, Pastan I, Puri RK (1995) Human glioma cells overexpress receptors for interleukin 13 and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and pseudomonas exotoxin. Clin Cancer Res 1:1253–1258
19. Della Bella S, Nicola S, Riva A, Biasin M, Clerici M, Villa ML (2004) Functional repertoire of dendritic cells generated in granulocyte macrophage-colony stimulating factor and interferon-alpha. J Leukoc Biol 75:106–116
20. Derynck R, Zhang YE (2003) Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 425:577–584
21. Dillman RO, Wiemann M, Oldham RK, Soori G, Bury M, Hafer R, Church C, DePriest C (1995) Interferon alpha-2a and external beam radiotherapy in the initial management of patients with glioma: a pilot study of the National Biotherapy Study Group. Cancer Biother 10:265–271
22. Dubost JJ, Rolhion C, Tchirkov A, Bertrand S, Chassagne J, Dosgilbert A, Verrelle P (2002) Interleukin-6-producing cells in a human glioblastoma cell line are not affected by ionizing radiation. J Neurooncol 56:29–34
23. Ehtesham M, Samoto K, Kabos P, Acosta FL, Gutierrez MA, Black KL, Yu JS (2002) Treatment of intracranial glioma with in situ interferon-gamma and tumor necrosis factor-alpha gene transfer. Cancer Gene Ther 9:925–934
24. Farkkila M, Jaaskelainen J, Kallio M, Blomstedt G, Raininko R, Virkkunen P, Paetau A, Sarelin H, Mantyla M (1994) Randomised, controlled study of intratumoral recombinant gamma-interferon treatment in newly diagnosed glioblastoma. Br J Cancer 70:138–141
25. Fillatreau S, Gray D, Anderton SM (2008) Not always the bad guys: B cells as regulators of autoimmune pathology. Nat Rev Immunol 8:391–397
26. Fiorentino DF, Bond MW, Mosmann TR (1989) Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med 170:2081–2095
27. Foxwell BM, Woerly G, Ryffel B (1989) Identification of interleukin 4 receptor-associated proteins and expression of both high- and low-affinity binding on human lymphoid cells. Eur J Immunol 19:1637–1641
28. Galizzi JP, Zuber CE, Harada N, Gorman DM, Djossou O, Kastelein R, Banchereau J, Howard M, Miyajima A (1990) Molecular cloning of a cDNA encoding the human interleukin 4 receptor. Int Immunol 2:669–675
29. Gehrmann J, Matsumoto Y, Kreutzberg GW (1995) Microglia: intrinsic immuneffector cell of the brain. Brain Res Brain Res Rev 20:269–287
30. George J, Banik NL, Ray SK (2009) Combination of hTERT knockdown and IFN-gamma treatment inhibited angiogenesis and tumor progression in glioblastoma. Clin Cancer Res 15:7186–7195
31. Groux H, Bigler M, de Vries JE, Roncarolo MG (1998) Inhibitory and stimulatory effects of IL-10 on human CD8+ T cells. J Immunol 160:3188–3193
32. Groves MD, Puduvalli VK, Gilbert MR, Levin VA, Conrad CA, Liu VH, Hunter K, Meyers C, Hess KR, Alfred Yung WK (2009) Two phase II trials of temozolomide with interferon-alpha2b (pegylated and non-pegylated) in patients with recurrent glioblastoma multiforme. Br J Cancer 101:615–620
33. Haque A, Banik NL, Ray SK (2007) Emerging role of combination of all-trans retinoic acid and interferon-gamma as chemoimmunotherapy in the management of human glioblastoma. Neurochem Res 32:2203–2209
34. Haque A, Das A, Hajiaghamohseni LM, Younger A, Banik NL, Ray SK (2007) Induction of apoptosis and immune response by all-trans retinoic acid plus interferon-gamma in human malignant glioblastoma T98G and U87MG cells. Cancer Immunol Immunother 56:615–625
35. Hau P, Jachimczak P, Schlingensiepen R, Schulmeyer F, Jauch T, Steinbrecher A, Brawanski A, Proescholdt M, Schlaier J, Buchroithner J, Pichler J, Wurm G, Mehdorn M, Strege R, Schuierer G, Villarrubia V, Fellner F, Jansen O, Straube T, Nohria V, Goldbrunner M, Kunst M, Schmaus S, Stauder G, Bogdahn U, Schlingensiepen KH (2007) Inhibition of TGF-beta2 with AP 12009 in recurrent malignant gliomas: from preclinical to phase I/II studies. Oligonucleotides 17:201–212
36. Hawrylowicz CM, O'Garra A (2005) Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. Nat Rev Immunol 5:271–283
37. Hayes RL, Koslow M, Hiesiger EM, Hymes KB, Hochster HS, Moore EJ, Pierz DM, Chen DK, Budzilovich GN, Ransohoff J (1995) Improved long term survival after intracavitary interleukin-2 and lymphokine-activated killer cells for adults with recurrent malignant glioma. Cancer 76:840–852
38. Heo DS, Yoon SJ, Kim WS, Lee KH, Seol JG, Lee SG, Jung CW, Cho EK, Kim CW, Park MH, Sung MW, Kim KH, Bang YJ, Kim NK (1998) Locoregional response and increased natural killer activity after intratumoral injection of HLA-B7/beta2-microglobulin gene in patients with cancer. Hum Gene Ther 9:2031–2038
39. Hirakawa K, Ueda S, Nakagawa Y, Suzuki K, Fukuma S, Kita M, Imanishi J, Kishida T (1983) Effect of human leukocyte interferon on malignant brain tumors. Cancer 51:1976–1981

40. Hjelmeland MD, Hjelmeland AB, Sathornsumetee S, Reese ED, Herbstreith MH, Laping NJ, Friedman HS, Bigner DD, Wang XF, Rich JN (2004) SB-431542, a small molecule transforming growth factor-beta-receptor antagonist, inhibits human glioma cell line proliferation and motility. Mol Cancer Ther 3:737–745
41. Hoffmann TK, Dworacki G, Tsukihiro T, Meidenbauer N, Gooding W, Johnson JT, Whiteside TL (2002) Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. Clin Cancer Res 8:2553–2562
42. Holladay FP, Heitz-Turner T, Bayer WL, Wood GW (1996) Autologous tumor cell vaccination combined with adoptive cellular immunotherapy in patients with grade III/IV astrocytoma. J Neurooncol 27:179–189
43. Honda K, Sakaguchi S, Nakajima C, Watanabe A, Yanai H, Matsumoto M, Ohteki T, Kaisho T, Takaoka A, Akira S, Seya T, Taniguchi T (2003) Selective contribution of IFN-alpha/beta signaling to the maturation of dendritic cells induced by double-stranded RNA or viral infection. Proc Natl Acad Sci USA 100:10872–10877
44. Hotfilder M, Knupfer H, Mohlenkamp G, Pennekamp P, Knupfers M, Van Gool S, Wolff JE (2000) Interferon-gamma increases IL-6 production in human glioblastoma cell lines. Anticancer Res 20:4445–4450
45. Hu S, Chao CC, Ehrlich LC, Sheng WS, Sutton RL, Rockswold GL, Peterson PK (1999) Inhibition of microglial cell RANTES production by IL-10 and TGF-beta. J Leukoc Biol 65:815–821
46. Huang AY, Golumbek P, Ahmadzadeh M, Jaffee E, Pardoll D, Levitsky H (1994) Role of bone marrow-derived cells in presenting MHC class I-restricted tumor antigens. Science 264:961–965
47. Huettner C, Paulus W, Roggendorf W (1995) Messenger RNA expression of the immunosuppressive cytokine IL-10 in human gliomas. Am J Pathol 146:317–322
48. Isaacs A, Lindenmann J (1957) Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 147:258–267
49. Jacobs SK, Wilson DJ, Kornblith PL, Grimm EA (1986) Interleukin-2 or autologous lymphokine-activated killer cell treatment of malignant glioma: phase I trial. Cancer Res 46:2101–2104
50. Jaffee EM, Pardoll DM (1997) Considerations for the clinical development of cytokine gene-transduced tumor cell vaccines. Methods 12:143–153
51. Jakowlew SB (2006) Transforming growth factor-beta in cancer and metastasis. Cancer Metastasis Rev 25:435–457
52. Joosten SA, Ottenhoff TH (2008) Human CD4 and CD8 regulatory T cells in infectious diseases and vaccination. Hum Immunol 69:760–770
53. Kim R, Emi M, Tanabe K (2006) Cancer immunosuppression and autoimmune disease: beyond immunosuppressive networks for tumour immunity. Immunology 119:254–264
54. Kioi M, Seetharam S, Puri RK (2008) Targeting IL-13Ralpha2-positive cancer with a novel recombinant immunotoxin composed of a single-chain antibody and mutated *Pseudomonas* exotoxin. Mol Cancer Ther 7:1579–1587
55. Kjellman C, Olofsson SP, Hansson O, Von Schantz T, Lindvall M, Nilsson I, Salford LG, Sjogren HO, Widegren B (2000) Expression of TGF-beta isoforms, TGF-beta receptors, and SMAD molecules at different stages of human glioma. Int J Cancer 89:251–258
56. Knight MJ, Riffkin CD, Muscat AM, Ashley DM, Hawkins CJ (2001) Analysis of FasL and TRAIL induced apoptosis pathways in glioma cells. Oncogene 20:5789–5798
57. Knupfer MM, Poppenborg H, Van Gool S, Domula M, Wolff JE (1997) Interferon-gamma inhibits proliferation and adhesion of T98G human malignant glioma cells in vitro. Klin Pädiatr 209:271–274
58. Knupfer MM, Knupfer H, Van Gool S, Domula M, Wolff JE (2000) Interferon gamma inhibits proliferation and hyaluronic acid adhesion of human malignant glioma cells in vitro. Cytokine 12:409–412
59. Knupfer MM, Knupfer H, Jendrossek V, Van Gool S, Wolff JE, Keller E (2001) Interferon-gamma inhibits growth and migration of A172 human glioblastoma cells. Anticancer Res 21:3989–3994
60. Kruse CA, Cepeda L, Owens B, Johnson SD, Stears J, Lillehei KO (1997) Treatment of recurrent glioma with intracavitary alloreactive cytotoxic T lymphocytes and interleukin-2. Cancer Immunol Immunother 45:77–87
61. Krushelnycky BW, Farr-Jones MA, Mielke B, McKean JD, Weir BK, Petruk KC (1991) Development of a large-animal human brain tumor xenograft model in immunosuppressed cats. Cancer Res 51:2430–2437
62. Kunwar S, Chang SM, Prados MD, Berger MS, Sampson JH, Croteau D, Sherman JW, Grahn AY, Shu VS, Dul JL, Husain SR, Joshi BH, Pedain C, Puri RK (2006) Safety of intraparenchymal convection-enhanced delivery of cintredekin besudotox in early-phase studies. Neurosurg Focus 20:E15
63. Le Bon A, Etchart N, Rossmann C, Ashton M, Hou S, Gewert D, Borrow P, Tough DF (2003) Cross-priming of CD8+ T cells stimulated by virus-induced type I interferon. Nat Immunol 4:1009–1015
64. Letterio JJ, Roberts AB (1998) Regulation of immune responses by TGF-beta. Annu Rev Immunol 16:137–161
65. Liu S, Yu Y, Zhang M, Wang W, Cao X (2001) The involvement of TNF-alpha-related apoptosis-inducing ligand in the enhanced cytotoxicity of IFN-beta-stimulated human dendritic cells to tumor cells. J Immunol 166:5407–5415
66. Ljungberg B, Grankvist K, Rasmuson T (1997) Serum interleukin-6 in relation to acute-phase reactants and survival in patients with renal cell carcinoma. Eur J Cancer 33:1794–1798
67. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109
68. Massague J (1998) TGF-beta signal transduction. Annu Rev Biochem 67:753–791
69. Matarrese P, Di Biase L, Santodonato L, Straface E, Mecchia M, Ascione B, Parmiani G, Belardelli F, Ferrantini M, Malorni W (2002) Type I interferon gene transfer sensitizes melanoma cells to apoptosis via a target activity on mitochondrial function. Am J Pathol 160:1507–1520
70. McGeer PL, Itagaki S, McGeer EG (1988) Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. Acta Neuropathol 76:550–557
71. Medawar PB (1948) Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. Br J Exp Pathol 29:58–69
72. Miettinen PJ, Ebner R, Lopez AR, Derynck R (1994) TGF-beta induced transdifferentiation of mammary epithelial cells to mesenchymal cells: involvement of type I receptors. J Cell Biol 127:2021–2036
73. Montoya M, Schiavoni G, Mattei F, Gresser I, Belardelli F, Borrow P, Tough DF (2002) Type I interferons produced by dendritic cells promote their phenotypic and functional activation. Blood 99:3263–3271
74. Moore KW, Vieira P, Fiorentino DF, Trounstine ML, Khan TA, Mosmann TR (1990) Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. Science 248:1230–1234

75. Moore KW, de Waal MR, Coffman RL, O'Garra A (2001) Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 19:683–765
76. Moqbel R, Ying S, Barkans J, Newman TM, Kimmitt P, Wakelin M, Taborda-Barata L, Meng Q, Corrigan CJ, Durham SR, Kay AB (1995) Identification of messenger RNA for IL-4 in human eosinophils with granule localization and release of the translated product. J Immunol 155:4939–4947
77. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136:2348–2357
78. Mut M, Sherman JH, Shaffrey ME, Schiff D (2008) Cintredekin besudotox in treatment of malignant glioma. Expert Opin Biol Ther 8:805–812
79. Nagai M, Arai T (1984) Clinical effect of interferon in malignant brain tumours. Neurosurg Rev 7:55–64
80. Nakagawa Y, Hirakawa K, Ueda S, Suzuki K, Fukuma S, Kishida T, Imanishi J, Amagai T (1983) Local administration of interferon for malignant brain tumors. Cancer Treat Rep 67:833–835
81. Nakahara N, Pollack IF, Storkus WJ, Wakabayashi T, Yoshida J, Okada H (2003) Effective induction of antiglioma cytotoxic T cells by coadministration of interferon-beta gene vector and dendritic cells. Cancer Gene Ther 10:549–558
82. Natsume A, Mizuno M, Ryuke Y, Yoshida J (1999) Antitumor effect and cellular immunity activation by murine interferon-beta gene transfer against intracerebral glioma in mouse. Gene Ther 6:1626–1633
83. Natsume A, Tsujimura K, Mizuno M, Takahashi T, Yoshida J (2000) IFN-beta gene therapy induces systemic antitumor immunity against malignant glioma. J Neurooncol 47:117–124
84. Natsume A, Ishii D, Wakabayashi T, Tsuno T, Hatano H, Mizuno M, Yoshida J (2005) IFN-beta down-regulates the expression of DNA repair gene MGMT and sensitizes resistant glioma cells to temozolomide. Cancer Res 65:7573–7579
85. Natsume A, Wakabayashi T, Ishii D, Maruta H, Fujii M, Shimato S, Ito M, Yoshida J (2008) A combination of IFN-beta and temozolomide in human glioma xenograft models: implication of p53-mediated MGMT downregulation. Cancer Chemother Pharmacol 61:653–659
86. Naumann U, Maass P, Gleske AK, Aulwurm S, Weller M, Eisele G (2008) Glioma gene therapy with soluble transforming growth factor-beta receptors II and III. Int J Oncol 33:759–765
87. O'Garra A, Vieira P (2007) T(H)1 cells control themselves by producing interleukin-10. Nat Rev Immunol 7:425–428
88. O'Garra A, Barrat FJ, Castro AG, Vicari A, Hawrylowicz C (2008) Strategies for use of IL-10 or its antagonists in human disease. Immunol Rev 223:114–131
89. Okada H, Kuwashima N (2002) Gene therapy and biologic therapy with interleukin-4. Curr Gene Ther 2:437–450
90. Okada H, Lieberman FS, Edington HD, Witham TF, Wargo MJ, Cai Q, Elder EH, Whiteside TL, Schold SC Jr, Pollack IF (2003) Autologous glioma cell vaccine admixed with interleukin-4 gene transfected fibroblasts in the treatment of recurrent glioblastoma: preliminary observations in a patient with a favorable response to therapy. J Neurooncol 64:13–20
91. Park LS, Friend D, Sassenfeld HM, Urdal DL (1987) Characterization of the human B cell stimulatory factor 1 receptor. J Exp Med 166:476–488
92. Parmiani G, Castelli C, Pilla L, Santinami M, Colombo MP, Rivoltini L (2007) Opposite immune functions of GM-CSF administered as vaccine adjuvant in cancer patients. Ann Oncol 18:226–232
93. Parney IF, Chang LJ, Farr-Jones MA, Hao C, Smylie M, Petruk KC (2006) Technical hurdles in a pilot clinical trial of combined B7-2 and GM-CSF immunogene therapy for glioblastomas and melanomas. J Neurooncol 78:71–80
94. Pepper MS (1997) Transforming growth factor-beta: vasculogenesis, angiogenesis, and vessel wall integrity. Cytokine Growth Factor Rev 8:21–43
95. Phillips LM, Lampson LA (1999) Site-specific control of T cell traffic in the brain: T cell entry to brainstem vs. hippocampus after local injection of IFN-gamma. J Neuroimmunol 96:218–227
96. Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE (1989) Mast cell lines produce lymphokines in response to cross-linkage of Fc epsilon RI or to calcium ionophores. Nature 339:64–67
97. Rajkumar SV, Buckner JC, Schomberg PJ, Cascino TL, Burch PA, Dinapoli RP (1998) Phase I evaluation of radiation combined with recombinant interferon alpha-2a and BCNU for patients with high-grade glioma. Int J Radiat Oncol Biol Phys 40:297–302
98. Ronnov-Jessen L, Petersen OW (1993) Induction of alpha-smooth muscle actin by transforming growth factor-beta 1 in quiescent human breast gland fibroblasts. Implications for myofibroblast generation in breast neoplasia. Lab Invest 68:696–707
99. Roussel E, Gingras MC, Grimm EA, Bruner JM, Moser RP (1996) Predominance of a type 2 intratumoural immune response in fresh tumour-infiltrating lymphocytes from human gliomas. Clin Exp Immunol 105:344–352
100. Rowbottom AW, Lepper MA, Garland RJ, Cox CV, Corley EG (1999) Interleukin-10-induced CD8 cell proliferation. Immunology 98:80–89
101. Santin AD, Hermonat PL, Ravaggi A, Bellone S, Pecorelli S, Roman JJ, Parham GP, Cannon MJ (2000) Interleukin-10 increases Th1 cytokine production and cytotoxic potential in human papillomavirus-specific CD8(+) cytotoxic T lymphocytes. J Virol 74:4729–4737
102. Santini SM, Lapenta C, Logozzi M, Parlato S, Spada M, Di Pucchio T, Belardelli F (2000) Type I interferon as a powerful adjuvant for monocyte-derived dendritic cell development and activity in vitro and in Hu-PBL-SCID mice. J Exp Med 191:1777–1788
103. Schiltz PM, Gomez GG, Read SB, Kulprathipanja NV, Kruse CA (2002) Effects of IFN-gamma and interleukin-1beta on major histocompatibility complex antigen and intercellular adhesion molecule-1 expression by 9L gliosarcoma: relevance to its cytolysis by alloreactive cytotoxic T lymphocytes. J Interferon Cytokine Res 22:1209–1216
104. Schlingensiepen KH, Schlingensiepen R, Steinbrecher A, Hau P, Bogdahn U, Fischer-Blass B, Jachimczak P (2006) Targeted tumor therapy with the TGF-beta 2 antisense compound AP 12009. Cytokine Growth Factor Rev 17:129–139
105. Schneider T, Becker A, Ringe K, Reinhold A, Firsching R, Sabel BA (2008) Brain tumor therapy by combined vaccination and antisense oligonucleotide delivery with nanoparticles. J Neuroimmunol 195:21–27
106. Segal BM, Glass DD, Shevach EM (2002) Cutting Edge: IL-10-producing CD4+ T cells mediate tumor rejection. J Immunol 168:1–4
107. Sidky YA, Borden EC (1987) Inhibition of angiogenesis by interferons: effects on tumor- and lymphocyte-induced vascular responses. Cancer Res 47:5155–5161
108. Sloan AE, Dansey R, Zamorano L, Barger G, Hamm C, Diaz F, Baynes R, Wood G (2000) Adoptive immunotherapy in patients with recurrent malignant glioma: preliminary results of using autologous whole-tumor vaccine plus granulocyte-macrophage colony-stimulating factor and adoptive transfer of anti-CD3-activated lymphocytes. Neurosurg Focus 9:e9

109. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996
110. Tada M, Diserens AC, Desbaillets I, de Tribolet N (1994) Analysis of cytokine receptor messenger RNA expression in human glioblastoma cells and normal astrocytes by reverse-transcription polymerase chain reaction. J Neurosurg 80:1063–1073
111. Thyrell L, Erickson S, Zhivotovsky B, Pokrovskaja K, Sangfelt O, Castro J, Einhorn S, Grander D (2002) Mechanisms of interferon-alpha induced apoptosis in malignant cells. Oncogene 21:1251–1262
112. Tran Thang NN, Derouazi M, Philippin G, Arcidiaco S, Di Berardino-Besson W, Masson F, Hoepner S, Riccadonna C, Burkhardt K, Guha A, Dietrich PY, Walker PR (2010) Immune infiltration of spontaneous mouse astrocytomas is dominated by immunosuppressive cells from early stages of tumor development. Cancer Res 70:4829–4839
113. Tran TT, Uhl M, Ma JY, Janssen L, Sriram V, Aulwurm S, Kerr I, Lam A, Webb HK, Kapoun AM, Kizer DE, McEnroe G, Hart B, Axon J, Murphy A, Chakravarty S, Dugar S, Protter AA, Higgins LS, Wick W, Weller M, Wong DH (2007) Inhibiting TGF-beta signaling restores immune surveillance in the SMA-560 glioma model. Neuro Oncol 9:259–270
114. Uhl M, Aulwurm S, Wischhusen J, Weiler M, Ma JY, Almirez R, Mangadu R, Liu YW, Platten M, Herrlinger U, Murphy A, Wong DH, Wick W, Higgins LS, Weller M (2004) SD-208, a novel transforming growth factor beta receptor I kinase inhibitor, inhibits growth and invasiveness and enhances immunogenicity of murine and human glioma cells in vitro and in vivo. Cancer Res 64:7954–7961
115. Vallieres L (2009) Trabedersen, a TGFbeta2-specific antisense oligonucleotide for the treatment of malignant gliomas and other tumors overexpressing TGFbeta2. IDrugs 12:445–453
116. Vaquero J, Martinez R (1992) Intratumoral immunotherapy with interferon-alpha and interleukin-2 in glioblastoma. Neuroreport 3:981–983
117. Velazquez JR, Lacy P, Mahmudi-Azer S, Bablitz B, Milne CD, Denburg JA, Moqbel R (2000) Interleukin-4 and RANTES expression in maturing eosinophils derived from human cord blood CD34+ progenitors. Immunology 101:419–425
118. Wakabayashi T, Hatano N, Kajita Y, Yoshida T, Mizuno M, Taniguchi K, Ohno T, Nagasaka T, Yoshida J (2000) Initial and maintenance combination treatment with interferon-beta, MCNU (Ranimustine), and radiotherapy for patients with previously untreated malignant glioma. J Neurooncol 49:57–62
119. Wakabayashi T, Natsume A, Hashizume Y, Fujii M, Mizuno M, Yoshida J (2008) A phase I clinical trial of interferon-beta gene therapy for high-grade glioma: novel findings from gene expression profiling and autopsy. J Gene Med 10:329–339
120. Watters JJ, Schartner JM, Badie B (2005) Microglia function in brain tumors. J Neurosci Res 81:447–455
121. Weber F, Asher A, Bucholz R, Berger M, Prados M, Chang S, Bruce J, Hall W, Rainov NG, Westphal M, Warnick RE, Rand RW, Floeth F, Rommel F, Pan H, Hingorani VN, Puri RK (2003) Safety, tolerability, and tumor response of IL4-*Pseudomonas* exotoxin (NBI-3001) in patients with recurrent malignant glioma. J Neurooncol 64:125–137
122. Williams LM, Ricchetti G, Sarma U, Smallie T, Foxwell BM (2004) Interleukin-10 suppression of myeloid cell activation—a continuing puzzle. Immunology 113:281–292
123. Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, Weller M, Wiendl H (2003) Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. Cancer Res 63:7462–7467
124. Wolff JE, Wagner S, Reinert C, Gnekow A, Kortmann RD, Kuhl J, Van Gool SW (2006) Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade glioma. J Neurooncol 79:315–321
125. Wrann M, Bodmer S, de Martin R, Siepl C, Hofer-Warbinek R, Frei K, Hofer E, Fontana A (1987) T cell suppressor factor from human glioblastoma cells is a 12.5-kd protein closely related to transforming growth factor-beta. EMBO J 6:1633–1636
126. Wu A, Wei J, Kong LY, Wang Y, Priebe W, Qiao W, Sawaya R, Heimberger AB (2010) Glioma cancer stem cells induce immunosuppressive macrophages/microglia. Neuro Oncol 12:1113–1125
127. Wynn TA (2003) IL-13 effector functions. Annu Rev Immunol 21:425–456
128. Yoshida J, Kajita Y, Wakabayashi T, Sugita K (1994) Long-term follow-up results of 175 patients with malignant glioma: importance of radical tumour resection and postoperative adjuvant therapy with interferon, ACNU and radiation. Acta Neurochir (Wien) 127:55–59
129. Yoshida J, Mizuno M, Fujii M, Kajita Y, Nakahara N, Hatano M, Saito R, Nobayashi M, Wakabayashi T (2004) Human gene therapy for malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) by in vivo transduction with human interferon beta gene using cationic liposomes. Hum Gene Ther 15:77–86
130. Yoshimoto T, Paul WE (1994) CD4pos, NK1.1pos T cells promptly produce interleukin 4 in response to in vivo challenge with anti-CD3. J Exp Med 179:1285–1295
131. Zou JP, Morford LA, Chougnet C, Dix AR, Brooks AG, Torres N, Shuman JD, Coligan JE, Brooks WH, Roszman TL, Shearer GM (1999) Human glioma-induced immunosuppression involves soluble factor(s) that alters monocyte cytokine profile and surface markers. J Immunol 162:4882–4892

Comments

Karl Frei, Zurich, Switzerland

In this review, the authors discuss aspects of cytokine networks in gliomas and attempt to provide some explanations for the poor successes of clinical trials using cytokine-based drugs or cytokine gene therapy.

The cross-talk between glioma cells and their immunological microenvironment leading to tumor-induced immunosuppression is addressed and the numerous factors involved discussed. Although the immunosuppressive effect of glioblastoma has long been recognized, the molecular basis for the cross-talk between tumor and immune cells remains still largely unknown. What is the underlying mechanism that allows a tumor to produce immunsuppressive factors that generate tolerogenic dendritic cells and regulatory T cells in the glioma microenvironment? Why are the innate immune cells (macrophages, natural killer cells, and neutrophils) incapable of killing glioma cells?

The definition of specific molecules and signalling pathways (e.g., signal transducer and activator of transcription 3, STAT3) that regulate the tumor microenvironment will provide important targets for cancer immunotherapy in the future.

Michael Weller, Zurich, Switzerland

Glioblastoma has been recognized as a paradigmatic neoplasm for the interaction of cancer cells with the host's immune system for decades. These tumors produce several cytokines not classically associated with astrocytic cells, including interleukins as well as

immunosuppressive, proinvasive, and angiogenic cytokines. This vast repertoire of soluble mediators allows for complex autocrine and paracrine interactions as well as a profound impact on the cells of the glioblastoma microenvironment. In this regard, it is important to note that, although glioblastomas do not possess a typical stroma like many neoplasms outside the nervous system, glioblastomas are still heavily infiltrated by non-neoplastic cells, including macrophages and microglial cells, reactive astrocytes, and immune cells from the periphery. The most important cytokines as of today appear to be (i) transforming growth factor-β which is at once strongly immunosuppressive, promigratory and proinvasive, and (ii) vascular endothelial growth factor which is considered the driving force of angiogenesis in these tumors. Future studies will have to clarify for each of these soluble factors the cellular source, the major cellular target, and the overall contribution to tumor progression versus tumor defense mechanisms. A deeper understanding of such interactions is required to fully exploit the potential of cytokines and cytokine-targeted therapeutic approaches to glioblastoma.