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Review Article

Immunotherapy in the Development of Anti-Tumor Immunity for the Treatment of a Brain Tumor

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Abstract:

Current management of patients with brain tumors include surgical resection, cranial irradiation and systemic or local chemotherapy. The treatments for these patients all have serious adverse side effects and the survival benefit is generally minimal for most patients. Understanding the impact of the immune system on cancer growth is becoming crucial for development of cancer vaccines and antitumor gene therapy strategies. Malignant cells express unique antigens which are the basis of clinical immunotherapeutic strategies. The antitumor immune response can be stimulated by cytokines such as IL-15 or IL-2. In this review studies with either a poxvirus augmented to secrete IL-15, or allogeneic fibroblasts engineered to secrete IL-2 are shown to be an effective treatment strategy in prolonging survival in mice with malignant intracerebral tumors upon injection of the treatment cells into the brain. Translation of these gene these gene therapy strategies for patients with intracerebral tumors are urgently needed.

keywords: gene therapy; brain tumors; immunotherapy; cancer vaccines

Introduction

Immune Mechanisms of Cancer Pathophysiology

The immune system has a dual nature; it can both inhibit tumor growth by the development of anti-tumor immunity or accelerate cancer progression by favoring tumor cells that can survive in an immunocompetent host along with conditions that support tumor growth [1,2]. There are times when the immune system unintentionally promotes tumor growth [3,4].

Immune Strategies of Cancer Therapy

Tumor cells express unique antigens which form the rationale for clinical immunotherapeutic strategies. A variety of immunotherapeutic strategies have been employed to treat cancer cells. These include immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy and oncogenic viruses [5]. Cancer vaccines attempt to activate the immune response against specific cancer cell antigens stimulating cytotoxic T lymphocytes to target cancer cells [6,7]. Vaccines have been prepared using antigen presenting dendritic cells stimulated with apoptotic bodies from tumor cells or tumor cell lysates. The introduction of tumor cell-derived RNA into dendritic cells is another approach which has been developed. Dendritic cells stimulated to respond to tumor antigens also results in the induction of immune responses against the broad array of tumor antigens expressed by the population of malignant cells including tumors of neuroectodermal origin [8,9]. In patients, immunization with autologous dendritic cells transfected with mRNA from malignant glioma cells elicited tumor-specific CD8+ cytotoxic T-lymphocyte (CTL) responses against the patient's malignant cells [10]. Novel and more specific targets such as glioma stem-like cells have been shown to increase the success of dendritic cell immunotherapy [11]. Although results of dendritic cell immunotherapy have demonstrated promise in animal models, clinical trials have revealed relatively short benefits or limited to a minority of treated patients with brain tumors [12].

Immunosuppression and Cancer Therapy

In many aggressive tumors, such as gliomas, progression is enabled by local immunosuppression driven by the accumulation of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) [13]. However, the mechanistic details of how Tregs and MDSCs are recruited in various tumors are not well understood. The poor response to treatment in patients with glioma may be due to the immunosuppressive T cells that usually prevent autoimmunity when the human immune response is evoked [14]. Regulatory T cells (Tregs) are immunosuppressive T cells that usually prevent autoimmunity when the human immune response is

evoked, and there has been a strong correlation between glioma-induced immunosuppression and Tregs. Agents which inhibit immune checkpoints are becoming another strategy for application of cancer therapy [15]. Immunosuppressive mediators such as IL-10, TGF-β and prostaglandin can block the function of the immune system and promote the growth of tumors, and inhibition of these immunosuppressive agents is one of the keys to success of tumor treatment [16].

Immunomodulatory Cytokines

There are a group of immunomodulatory cytokines including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 which belong to the family of four α-helix bundle cytokines [17]. The development of IL-2 has been a significant force in the development of immunotherapy in cancer [18]. Recombinant IL-2 can induce clinical responses in up to 15% of patients with metastatic cancer. However, the use of IL-2 is limited by toxic side effects and the stimulation of regulatory T cells which modulate the immune system. To overcome these limitations and improve response rates, other agents which stimulate T cells such as IL-15 have been in clinical development. Furthermore IL-15, unlike IL-2, does not contribute to the maintenance of regulatory T cells [19,20]. Co-expression of IL-15 with the sushi domain of the alpha subunit of Il-15Rα greatly enhances IL-15 stability and function in vivo. Pre-association of IL-15 with IL-15Rα generates a more portent ligand compared to the cytokine alone. Natural killer (NK) cells are a crucial element of the immune system. NK cell immunity is largely regulated by interleukin-15 [21]. IL15 can activate and attract natural killer cells and CD8+ cells along with promoting the development of memory T cells. Genetic modification of NK cells to produce IL-15 has been explored [22]. Structurally similar to interleukin 2, IL-15 supports the persistence of CD8+ memory T cells while inhibiting IL-2-induced T cell death to better maintain long-term anti-tumor immunity [23]. NK cell infusion along with Il-15 in combination with checkpoint inhibitors has been examined. The clinical use of IL-15 has been limited by dose-limiting toxicities [24]. A tumor-conditional IL-15 (pro-IL-15) has been developed which demonstrates significantly reduced toxicity but uncompromised antitumor-efficacy. Pro-IL-15 can overcome checkpoint blockade resistance and actual adoptive T cells which can lead to eradication of certain advanced tumors. However, initial results have not demonstrated efficacy for prolonging survival in patients with brain tumors treated with various cytokines alone including IL-2 or IL-15 [25].

Principles of Brain Tumor Immunotherapy

Dendritic cells stimulated with tumor antigens represent a significant immunotherapeutic approach that has demonstrated potential in brain tumor animal models, but clinical trials involving dendritic cells have documented relatively short benefits which are limited to a small number of patients treated with brain tumors [26]. In many aggressive tumors, such as gliomas, progression is enhanced by local immunosuppression driven by the accumulation of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) that normally prevent anti-tumor immunity when the immune response is stimulated [27,28].

Potential Application of Oncolytic Viruses in Brain Tumor Therapy

Oncolytic viruses, either engineered or in nature, may selectively infect and lyse tumor cells while not infecting normal cells [29]. Once oncolytic viruses infect tumor cells, they may be involved in the anti-tumor response by a direct cytotoxic effect on tumor cells and consequent release of tumor-associated antigens leading to the stimulation of anti-tumor immune responses [30]. When the virus is engineered to express an immunostimulatory cytokine [31], it also may lead to the release of the expression of potent immune-activating agents which may attract anti-tumor immune cells into the tumor microenvironment.

IL-15 and Oncolytic virus as a Potential Treatment for a brain tumor

The use of oncolytic viruses engineered to secrete cytokines has the potential to develop a potent antitumor immune response, and this strategy has been explored for the treatment of patients with high grade gliomas, particularly with IL-2 and IL-15 [32]. A potential advantage of IL-15 is that there is less activation of immune inhibitory Tregs associated with this cytokine. Several treatment strategies involving cytokine expressing treatment cells have recently been reported [33]. Prolongation of survival was found with mice bearing an intracerebral glioma treated intracerebrally with an oncolytic poxvirus (myxoma virus) expressing the fusion protein IL15Rα-tdTr as the T cell activating stimulus in combination with a prostaglandin synthesis inhibitor to block immunosuppression (celecoxib) supplemented by adoptive T-cell therapy (tumor-specific CD8+ T cells) [34,35]. Rapamycin was also used to enhance the spread and replication of the oncolytic virus [36,37]. An increased number of infiltrating NK and CD8+ T cells was detected in the tumor specimens indicating that the IL15Rα-IL15 fusion protein is biologically functional and could attract NK and CD8+ T cells into the tumor site. The rationale for this treatment strategy is that the oncolytic poxvirus may lead to a direct cytotoxic effect on glioma cells and consequent release of potential tumor antigens which may result in the stimulation of an anti-tumor immune response. When the virus is engineered to express a cytokine, it also becomes a vector for local expression of potent immune-activating agents. In this study IL15 was chosen because it activates and maintains the function of NK and CD8+ T cells [38)] with less activation of Tregs [39,40]. Systemic inflammation can occur upon parenteral delivery of this cytokine but has not been observed following introduction of IL15 into the brain. However, limited efficacy (short of statistical significance) was observed when mice bearing intracerebral glioma were treated with myxoma virus genetically engineered to express IL15 as a single treatment without other agents.

Allogeneic Fibroblasts Engineered to Secrete IL-2 as a Treatment of a Brain Tumor

The use of fibroblasts genetically engineered to secrete certain cytokines is another attractive method for tumor therapy. The intracerebral injection of cytokine secreting cells has not been shown to have significant long-term side effects. Allogeneic rather than syngeneic cells were chosen for local cytokine administration because of the known adjuvant effects of foreign MHC determinants on the antitumor response and the likelihood that the cells would be rejected by cellular immune mechanisms. Allogeneic IL-2 secreting fibroblasts have been found to prolong survival when injected intracerebrally into mice with an established intracerebral glioma (Gl261) or breast carcinoma (SB-5b) [41]. Spleen cell analysis revealed that the cellular antitumor response was found to be mediated predominantly by natural killer/lymphokine-activated killer and CD8+ cells. Experiments involving the treatment of animals with an intracerebral tumor using subcutaneous injections of IL-2 secreting allogeneic fibroblasts demonstrated no effect on prolonging survival despite the development of a vigorous anti-tumor immune response. Of special interest mice injected intracerebrally with the cytokine-secreting allogeneic fibroblasts alone exhibited no neurologic defect and there was no adverse effect on survival In order to enhance the antitumor immune response with allogeneic fibroblasts, a vaccine was prepared by transfer

of a cDNA expression library derived from tumor cells into an allogeneic mouse fibroblast cell line expressing a cytokine such as IL-2. These cells were found to have significant potential in the development of an antitumor immune response and prolongation of survival in mice with an intracerebral tumor following injection of the treatment cells into the brain [42]. The allogeneic fibroblasts transfected with tumor DNA should stimulate the expression of tumor antigens. The transferred DNA integrates spontaneously into the genome of the recipient cells and replicates as the cells divide. This subsequently results in the development of immunity to antigens that characterize the patient's tumor. Only small amounts of tumor tissue are necessary to enable treatment at an early stage of the disease, when tumor tissue may be available in limited amounts and the tumor is most susceptible to immune based therapy. The effect of antibodies against various T-cell subsets on the responding T cell response was used to determine the types of cells activated for antitumor immunity in the spleens of mice injected into the tumor bed with treatment cells. ELISPOT IFN- assays were used for this analysis. The antitumor immune response was inhibited to the greatest extent by antibodies against CD4+ cells. The results were less dramatic if the spleen cells were incubated in the media containing CD8+ or NK/LAK antibodies. Finally, a unique enrichment strategy has also been developed to increase the proportion of immunotherapeutic cells in the vaccine.

Pre-Clinical Animal Models

It has been reported that IFN-γ secretion and cell cytotoxicity of natural killer (NK) cells are profoundly suppressed [43], the number of cytotoxic T cells and T helper cells [44] are markedly decreased while the number of regulatory T cells (Tregs) [45,46] and low-density neutrophils are significantly increased in the postoperative period. All these factors could contribute to the poor prognosis and recurrence of tumor following surgical resection. As a preliminary step toward testing a novel immunotherapeutic strategy, studies were done to determine whether mice can survive resection of an advanced murine glioma. In these studies, C57BL/6 mice were implanted with 5 X 104 GL261 glioma cells into the right frontal lobe and then underwent tumor resection under a high-powered microscope after 16 days. An attempt was made to resect as much tumor as possible. No neurologic deficits were observed in the animals in this study. The results revealed that the advanced glioma occupied about 25% of the right hemisphere and the surgical resection revealed that 85% of the tumor was removed [47]. The survival curve showed that the median survival for the resected mice was prolonged by 5 days although this was short of significant statistical difference. The results indicate that it is feasible to perform tumor resection of mice bearing advanced glioma in the brain, mice can survive from the resection, and the surgical resection has the potential to prolong survival time. It was subsequently investigated whether tumor resection followed by immunotherapy treatment would lead to a prolongation of survival without adverse side effects. In these studies, C57Bl/6 mice were implanted with 5 X 104 GL261 glioma cells into the right frontal lobe and then underwent tumor resection under a high-powered microscope 16 days after tumor implantation. The mice were then treated with an oncolytic poxvirus (myxoma virus) expressing the fusion protein IL15Rα-tdTr as the T cell activating stimulus in combination with a prostaglandin synthesis inhibitor to block immunosuppression (celecoxib) and supplemented by adoptive T-cell therapy (tumor-specific CD8+ T cells). Rapamycin was also used to enhance the spread and replication of the oncolytic virus. The results, however, revealed no significant prolongation of survival in the treated mice. This is likely because the resection was not done until 16 days after tumor implantation and the potential to prolong survival would probably be more effective if the treatment was initiated at an earlier stage following tumor implantation.

Conclusion

The goal of tumor treatment would be the eradication of every tumor cell. It is unlikely that a single therapy can achieve this goal in the case of most tumors. Gliomas infiltrate into the brain and it can be difficult to distinguish tumor tissue from normal brain. Therefore, surgical treatment for these tumors is not generally efficacious and the survival of these patients remains poor. In addition, these tumors remain resistant to standard additional treatment modalities including radiation therapy and chemotherapy, and these treatments are associated with significant adverse side effects. It is possible that surgical treatments can be improved using bioluminescent imaging which can help to identify residual tumor cells. Alternatively, intraoperative imaging such as CT or MRI can help in this regard although aggressive surgical treatment can lead to neurologic deficits. In the studies described in his report using immunotherapy strategies no neurologic deficits have been observed. Cancer vaccines have demonstrated ability to stimulate a strong antitumor immune response but significant challenges in achieving clinical efficacy have been encountered. Immune system tolerance can weaken the immune system's reaction to cancer cells. Regulatory T cells and myeloid-derived suppressor cells can impede the antitumor immune response against the tumors. The use of cytokines is becoming more common in treatment of patients with high grade tumors, particularly with IL-2 and IL-15. A potential advantage of IL-15 is that this cytokine activates and maintains the function of NK and CD8+ T cells, but there is less activation of immune inhibitory Tregs. Novel treatments are urgently needed to treat brain tumors.

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