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Mini Review

Unique and Specific Antigenicity of High Grade Gliomas are Essential and Direct Derivatives of the Specific Genesis in Malignant Transformation of Neoplasms in General

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Abstract

Dimensions of non-resolution of a given high-grade glioma necessitate the identification and isolation of specific tumor antigens on the surface of the glioma cells in a manner that actively endows the progressiveness of injury to the tumor cells. In such manner, exquisite targeting should be recognized as compatible with the proposed dynamics of a series of immunotherapeutic modalities within the expanding growing regions of glioma evolution. These induce systems of response as dictated by cytotoxic lymphocytes. In terms beyond the simple concept of reappraisal and also in terms of mechanistic delivery of such cytotoxic lymphocytes, the antigenicity of individual glioma cells is paramount driver also for the initial oncogenic emergence of the neoplastic cells. These are further dictated by evolutionary themes in expansion and spread of the high-grade gliomas.

Keywords: Antigenicity; High grade gliomas; Neoplasms; Cytotoxic lymphocytes

Introduction

Stimulator and responding cytotoxic lymphocytes have been utilized in a Major Histocompatibility Antigen restricted manner in an attempt to cyto-reduce glioma cells within anaplastic astrocytoma and glioblastoma tumors intracranially and intra-thecally. Dendritic cells are the body's most professional antigen-presenting cells in activating T cells to stimulate an adaptive immune response [1]. The phenomenona of response in clinical trials have been tentatively examined in the hope of prolongation of patient survival and for clinico-pathologic response as assessed by magnetic resonance imaging and by clinical neurologic examinations. The overt clinical response has been improved by utilizing specifically activated cytotoxic cells in contrast to nonspecifically activated lymphocytes as induced by CD3 or lectin.

Genetically engineered T-cells such as chimeric antigen receptor T cells have the potential to attack highly infiltrative tumors in a tumor specific manner with possible persistence of the adaptive immune response [2].

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The utilization of Interleukin 2 has allowed the expansion of lymphocyte draining nodes to improve delivery of increased reactive cytotoxic cells either by intracavitary delivery intra tumorally at surgery or by employed a Richman reservoir placed subgaleally at surgical tumor debulking.

The progression of tumor growth from residual tumor bed deposits was assessed post operatively. CD133-positive tumor cells constitute cells that confer glioma radio-resistance; targeting DNA damage checkpoint response in cancer stem cells may overcome this radio-resistance [3]. The onset dynamics of such treatment necessitates improvement in delivery in view of the partial immune privileged status of the Central Nervous System (CNS). Improvement by enhancement of the infiltrative capabilities of the delivered cytotoxic lymphocytes in the intratumoral neuropil is a necessary requirement in inducing activation of both stimulator and responding lymphocytes that are delivered to the tumor lesion. Clarification of the molecular mechanism in glioma progression is critical for effective glioma treatment; melanoma-associated antigen A2 is over expressed in glioma cells and related to prognosis [4].

Complexity

T-lymphocytes play a central role in cancer vaccination; several antigenic peptides of human tutors are identified and can now be artificially manipulated [5]. The complexity of activation mechanisms has also provoked the utilization of Interferon-gamma in an attempt to increase the MHC molecules on tumor cells. In such terms, the onset and progression of specifically activated cytotoxic lymphocytes are theoretically enhanced with propagation of cyto-reducing effect within the high grade gliomas.

Cultures

It is further to such considerations that ex vivo cultures would expand the number of cytotoxic lymphocytes by co-culture with

irradiated autologous glioma cells and with the addition of low doses of Interleukin 2. The development of increments in response has been evidenced in a small number of treated patients in clinical trials, with reduction in size of the treated glioma or even as apparent cure of the patient.

Tumor infiltrating lymphocytes and programmed death ligand 1 are targets of immune checkpoint inhibitors [6]. Several cancer-testis antigen include novel genes have been detected in high-grade primary cell lines [7].

The evolutionary nature of neoplastic lesions of glioma derivation is a complex series of dimensions that requires the institution of multiple infusions of the cytotoxic lymphocytes intratumorally. Also, clinical complications or side effects have to be closely monitored especially within the 24 hour period after infusion of autologous or alloreactive culturally expanded cytotoxic lymphocytes. It is with the view to optimization of such preparations and product derivatives that peripheral blood mononuclear cells from leukopaks have also been utilized in terms of delivery of the stimulator and responding cells to the gliomas.

A relationship exists between HLA-F expression and clinical prognosis in gliomas [8].

Alloreactive lymphocyte preparations include different MHC antigens to better enhance reactivity of the cytotoxic lymphocytes to the specifically targeted glioma cells. The conceptual micro-environment of the high grade glioma is a shifting antigenic pool within systems of stimulation and response. Allogeneic lymphocyte preparations are theoretically optimal delivery system agonists in the attempt to better utilize reactivity potential to cyto-reduce the glioma cell population. In such terms, derivative potentials for specifically activated lymphocytes require the identification and isolation of individual antigens that are specific for only the glioma cells. Such specific tumor antigens are essential for the targeting mechanics in terms of stimulation of immune tumor cell surveillance in a manner that fundamentally redefines the dual stimulator and responding cytotoxic cell delivery systems.

Sequential delivery of Interferon-alpha gene and dendritic cells to intracranial glioma enhances an effective antitumor response [9].

Antigenicity

The search for a unique set of tumor antigens is rendered difficult because of the often-limited number of tumor tissue cells that can be harvested and also because of the often present foci of tumor necrosis in high grade gliomas. Replication-defective adenoviral vectors are promising vaccine candidates for diseases that require song CD8(+) T-cell responses for protection [10]. Dendritic cells are potent antigen-presenting cells that play a critical role in the initiation of host immune responses against tumor antigens [11]. Immunotherapy using dendritic cells or peptide vaccines successfully induce an antitumor immune response and prolong survival without major side effects in glioma patients [12]. In such terms, the problem of identification of unique tumor antigens renders the requirement of an essential personalized patient approach in managing these patients with measures central to glioma immunotherapy.

Concluding Remarks

Dynamics of reproducibility of immune attack strategies incur the necessary recognition of tumor specific antigens with contrasting profiles of peripheral neoplastic lesions such as melanoma that shares with gliomas a neuro ectodermal derivation.

In such terms, the ongoing attempts at identification of such specificity profiles of tumor antigenicity is further rendered difficult by the emerging recognition of the minor nature of most unique tumor cell antigens so far identified. The lack of functional dendritic cells from the brain induces the brain to be deficient in priming systemic immune responses to glioma antigens [13].

The incremental infiltrativeness of the high grade glioma cells is an added implemented attribute necessary to the delivery of cytotoxic responding lymphocytes that mechanistically must come in contact with the neoplastic cells. Hence, especially with locally inaccessible tumor lesions that are beyond surgical debulking, the onset and progression of immunotherapeutic agonist systems within the gliomas render an essential elemental measure to be instituted as delivery mechanics. Pre-clinical studies in glioblastoma induce long-term tutor survival and immunologic memory in murine models with stimulation of dendritic cell activity with various antigens and co-stimulatory molecules [14]. Targeting receptors of dendritic cells to enhance cancer antigen loading through an antibody-mediated antigen uptake process is a promising cancer immunotherapeutic mechanism [15].

The specific incremental nature of glioma cell proliferation and spread necessitates the provision of dynamic cytotoxic cells that specifically target tumor cells in a manner beyond simple concepts of malignant cell spread. The immunosuppressive microenvironment is a major factor enhancing the growth of glioblastoma [16].

It is in view of such dynamics that a combinatorial complex system utilizing synergism and self-promotion of reactivity to unique tumor antigens must be employed within the settings of also conventional surgical management coupled to radiotherapy and chemotherapy.

The various profile coordinates recognizably necessitate the institution of lesion control within conditioned profiles of high tumor cell turnover and also of the specific hallmarks of evolutionary antigenicity change as theoretically exhibited by high-grade gliomas.

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