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Letter to the Editor

Immunotherapy in gliomas: Are we reckoning without the innate immunity?

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Abstract

Innate immunity plays a central role in neoplasms, including those affecting the central nervous system (CNS). Nowadays, tumors classification, especially that regarding gliomas, is based on molecular features such as mutations in isocitrate dehydrogenase (IDH) genes and the presence of co-deletion 1p/19q. Therapy, in most cases, is based on surgery, radiotherapy, and pharmacological treatment with chemotherapeutic agents such as temozolomide. However, the results of the treatments, after many decades, are not completely satisfactory. There is a class of drugs, used to treat cancer, which modulates immune response; in this class, the immune checkpoint inhibitors and vaccines play a prominent role. These drugs were evaluated for the treatment of gliomas, but they exhibited a poor outcome in clinical trials. Those scarce results could be due to the response of tumor-associated macrophage that creates imbalances between innate and adaptive immunity and changes in blood–brain barrier properties. Here, we have briefly reviewed the current literature on this topic, focusing on the possible role for innate immunity in the failure of immunotherapies against brain tumors.

Keywords

glioblastoma, immunotherapyinnate immunity, macrophage polarization, neoplasm staging, tumor-associated macrophages

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Introduction

Gliomas are one of the categories that have undergone the most profound variations in the brain tumors classification by World Health Organization (WHO) in 2016. In the past, many mutations in many genes have been described as related to the development of glial neoplasms.[1,2] However, the authors of the aforementioned classification essentially focused on the isocitrate dehydrogenase 1 (*IDH-1*) or *IDH-2* gene mutations, ordering the various entities, mainly for prognostic reasons. The practical benefits from a therapeutic point of view are imperceptible so far, since the prognosis, primarily for high-grade forms such as glioblastoma, remains very poor. Furthermore, diagnostic practices applied to individual entities can be tricky or too expensive and therefore not applicable throughout the world. In recent years, various strategies of immunotherapy have been proposed for central nervous system (CNS) tumors, but results seem to be quite disappointing so far.

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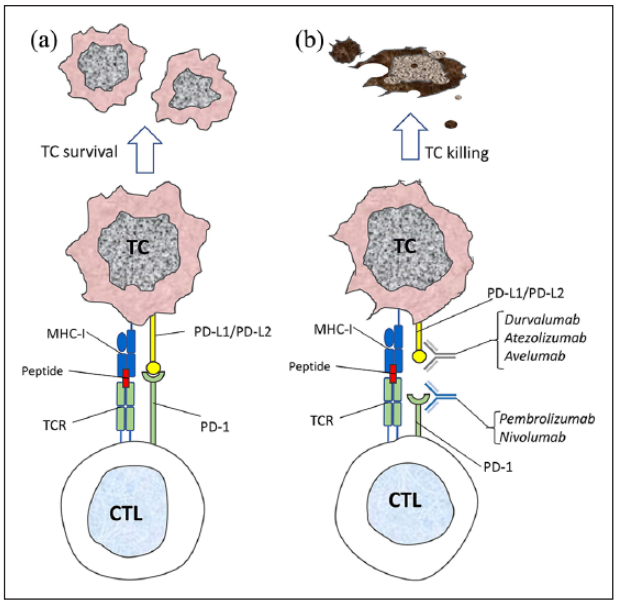

Figure 1. Mechanism of action of immunotherapic drugs: (a) tumor cells (TC) express the transmembrane protein, programmed death ligand-1 (PD-L1) or PD-L2. The binding of PD-L1 or PD-L2 to its receptor PD-1, found on T cells, transmits a signal that inhibits the T-cell receptor (TCR)-mediated activation and proliferation of the T cells. This signaling mechanism allows the evasion from anti-tumor response and (b) the FDA-approved immunotherapic drugs durvalumab, atezolizumab, and avelumab consist of human monoclonal IgG1 directed against PD-L1 or PD-L2. Pembrolizumab and nivolumab are humanized mouse IgG4 monoclonals that target PD-1. These kinds of drugs are called immune checkpoint inhibitors (ICIs).

The aim of this work is to briefly discuss the role of innate immunity as a possible cause of failure of immunotherapy facing brain tumors.

Methods and results

Pertinent studies published from January 2004 to September 2018 were selected by means of a MEDLINE search, accessed via PubMed database scanning. Search keys like "Innate immunity and brain tumors," "immunotherapy and brain tumors," and "Macrophages and brain tumors" gave an output of 2578 items. The articles we decided to cite in this article were chosen based on their overall significance, referring to a couple of criteria. First, we took into account the recent appearance namely for the ability to better represent the state of the art describing subjects involved in the studies, and second, we considered the exemplary value on the subjects dealt with, such as innate immunity or brain tumors. The main results we could summarize from literature reviewing would be the messages that immunotherapy cannot be considered yet a safe tool for therapy against brain tumors and that innate immunity could exert a critical influence in the real efficacy of this kind of treatments.

Discussion

Current classification of diffuse gliomas is based on *IDH*s genes mutation and 1p/19q co-deletion. Generally, glioblastomas, oligodendrogliomas, and astrocytomas are treated combining radiotherapy and chemotherapy, making this approach more effective. Differentiated protocols are applied regarding *IDH* mutation status.[3]

The currently used immunotherapeutic tools against brain cancers are based on immune checkpoint inhibitors (ICIs) and vaccine-mediated immunization. ICIs consist of monoclonal antibodies that neutralize immunosuppressive signaling and enhance immune responses against tumor cells targeting costimulatory and inhibitory molecules, which can regulate the activation and effector functions of T lymphocytes (Figure 1). Under physiological conditions, those regulatory circuits are essential for self-tolerance, but in many cases, they may be coopted in malignancies. ICIs such as pembrolizumab and nivolumab are anti-programmed cell death protein-1 (PD-1); durvalumab, atezolizumab, and avelumab are anti-programmed cell death ligand-1 (PD-L1); and ipilimumab is anti-cytotoxic T lymphocyte–associated protein 4 (CTLA-4). All these preparations have shown a discrete efficacy in clinical trials.

However, in a Phase 3 study focusing on recurrence of glioblastoma, the treatment with nivolumab failed to increase overall survival compared to the treatment with bevacizumab that targets vascular endothelial growth factor A (VEGF-A). Furthermore, in patients with recurrent high-grade gliomas, salvage therapy with nivolumab or pembrolizumab did not significantly improve survival.[4] Two proposals for explanations can be advanced: the former is that not always in glioblastomas, there is a sufficient number of PD-1 receptor expressing cells[5], and second, there could be an active role of the neoplasm populating innate immunity cells (Figure 2(a) and (b)).

Ipilimumab and tremelimumab are CTLA-4 targeting monoclonal antibodies currently being

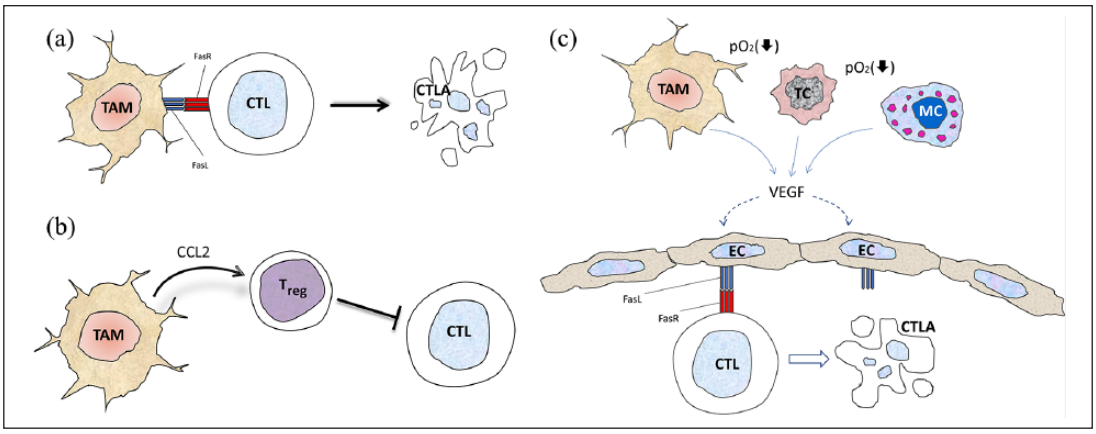

Figure 2. Direct and indirect action of TAMs and hypoxia-driven immunosuppressive dynamics in glioma microenvironment: (a) cytotoxic lymphocytes (CTL) could be led on to apoptosis through the interaction FasL/FasR expressed on TAMs and CTL, respectively, (b) alternative polarized TAM by secreting chemokine such as CCL2 are able to recruit T_{reg} cells inside the tumor microenvironment and these suppressor T cells inhibit CTL, and (c) hypoxia can induce several cell types to secrete vascular endothelial growth factor (VEGF) among which are tumor cells (TC), tumor-associated macrophages (TAM), and mast cells (MC). VEGF, in turn, can induce the expression of membrane-anchored Fas ligand (FasL) on the vascular endothelium during angiogenesis. The interaction between FasL and Fas receptor (FasR) or CD95 drag CTL toward the apoptotic program.

tested in glioblastoma immunotherapy. In a clinical trial, the concomitant use of ipilimumab and bevacizumab, in patients with malignant glioma, culminated in partial radiographic response for 31%. Tremelimumab, in combination with durvalumab (AstraZeneca), is under investigation as a combined treatment against a variety of solid tumors, including recurrent glioblastoma (NCT02794883).[5] These unfavorable data for ICI-based immunotherapy could be explained by already known mechanisms of resistance. VEGFs can be produced by glioma tumor cells, and also by polymorphonuclear neutrophils, macrophages, and endothelium, during angiogenesis (Figure 2(c)), and it can result in apoptosis induction of CD8 T-effector cells that enter the tumor tissue.[5]

Interestingly, the number of infiltrating neutrophils correlates with glioma grade and with acquired resistance to anti-VEGF therapy in glioblastoma multiforme (GBM).[6] M2-polarized macrophages have a higher angiogenic potential compared to M1. Tumor-associated macrophages (TAMs) are, as a rule, alternatively polarized toward an M2 state. Both M1 and M2 macrophages can produce VEGF, and IL-10 secretion and hypoxia, present in high-grade gliomas microenvironment, enhance it.[7] Even mast cells are powerful producers of IL-10 and angiogenetic factors[8] conditioning, similar to the macrophage phenotype.[9]

FasL and PD-L1 are expressed both on glioma cells and TAMs surface T cell inhibition and apoptosis (Figure 2(a)). Both tumor-infiltrating macrophages and microglia are reported to express high levels of PD-L1 in GBMs. This implies that an important fraction of administered immunotherapeutic antibodies might target macrophage population rather than tumor cells (Figure 3(a)); microglia account for 50% of the FasL expressing cells in gliomas and may be considered a major cause for the induced apoptosis of lymphocytes[5] (Figure 2(a)). In astrocytic neoplasms, the greater the tumor grade, the more increase in tumor mass and the percentage of TAMs increases in parallel, up to 70% of tumor mass, as it can be observed in glioblastoma.[5] The state of macrophage polarization can move from M1 to M2 while the tumor grade is increasing.[7] It is probable that failure of ICIs therapy in higher grade glial tumors could be due to a direct action of macrophages against the lymphocytic population, hired to kill neoplastic cells.

Immunization strategies with tumor-associated or tumor-specific antigens can increase the immune response facing tumor, and it has also been explored against gliomas. TAMs and microglia shall support tumor progression, uptaking the injected antigens or released by glioblastoma tumor cells (Figure 3(b)). Indeed, TAMs, by producing CCL2, are also able to recruit lymphocytes with immunosuppressive activity such as T_{reg} cells, or they directly inhibit tumoricidal T cells by means of receptors and ligands usually targeted by ICIs[5] (Figures 2(b)

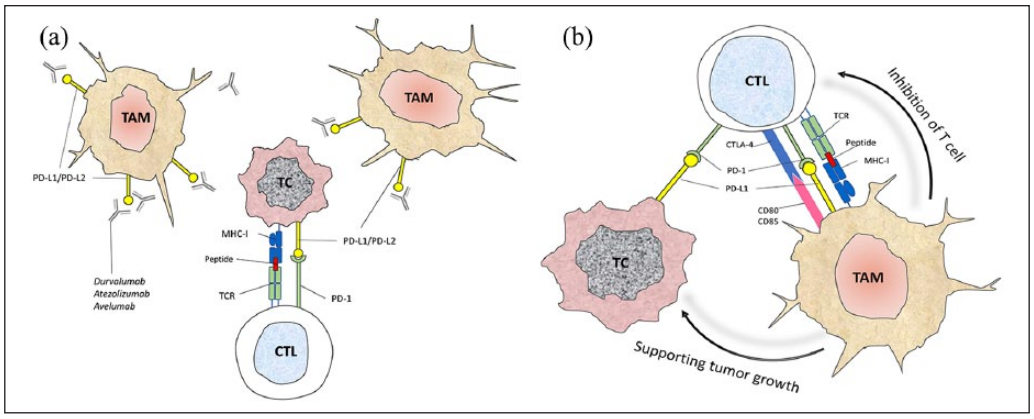

Figure 3. Potential mechanisms contributing to immunotherapy and tumor vaccination failure (a) programmed death ligand 1 and/or 2 (PD-L1/PD-L2) are commonly expressed on the surface of dendritic cells or macrophages. Tumor-associated macrophages (TAM) can become the prevalent cell population on glioma tissue. This leads to a heavy reduction of the immunotherapy drugs that could target tumor cell inhibitory interactions with cytotoxic T cells (CTLs) and (b) cooperative action between tumor cells (TC) and tumor-associated macrophages (TAM) to tumor escape from immune surveillance. Activated cytotoxic T lymphocyte (CTL) could be inhibited by tumor cells through a repressive signaling, triggered by PD-1/PD-L1 interaction. TAMs can concur to it, routing the same immunosuppressive signal by the same receptor/ligand interaction and, additionally, can reinforce it with a supplementary inhibitory signal to specific CTL for tumor antigens. This last signal is channeled via binding of CD80 and/or CD85, expressed on TAMs surface, with CTLA-4 (cytotoxic T lymphocyte antigen 4) expressed on CTL surface.

and 3(b)). Some, among the mechanisms that would make ICIs treatments ineffective, could be responsible for vaccination failure just because, in any case, cytotoxic T lymphocytes are the terminal effectors.

In conclusion, the cells of innate immunity, such as macrophages, mast cells, and neutrophils, can somehow negatively interfere with the action of ICIs or immunized lymphocytes against tumor antigens. This is the reason why macrophage re-education might be an interesting strategy in order to support ICI or vaccine therapies. Also, it must be considered that future therapeutic intervention, targeting mast cell activity, hypothetically could provide another tool in this scenario.[5,9,10]

Generally speaking, a possible future direction for research in the therapy of brain tumors could be the molecular and immunological targeting of the innate immune system.

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