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Impact of General Factors on Glioma Immunotherapy

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Glioma remains the most common malignant tumor in the brain and is also the most difficult to treat. Immunotherapy achieving long-lasting tumor remission in multiple cancer types has received considerable attention due to its potential to improve the treatment outcomes of patients with glioma. However, clinical trials have not yet demonstrated major improvements in prognoses, which might be attributable to the extrinsic components and intrinsic mechanisms involved in the tumor microenvironment and immune system. It is particularly noteworthy that there is emerging evidence that current routine treatment modalities and the physical and psychological characteristics of patients have different impacts on the efficacy of glioma immunotherapy. This article addresses how these factors interact with the host immune system and tumor microenvironment, and highlights their potential roles in glioma immunotherapy, with the ultimate goal of developing better immunotherapy-based personalized medicine strategies.

Keywords glioma; immunotherapy; standard of care; psychophysiological characteristics.

INTRODUCTION

Gliomas are the most common neuroepithelial tumor in the central nervous system, and they are classified according to their phenotypic and genotypic characteristics into grades I–IV by the World Health Organization.[1] Glioblastoma (GBM) with wild-type IDH is a grade-IV tumor characterized by considerable aggressiveness, and it remains one of the most lethal cancers in human. Despite multiple treatment modalities being available, including maximal safe surgical resection, adjuvant radiation with temozolomide (TMZ) chemotherapy, and alternating tumor-treating fields (TTFields) therapy, patients with GBM have a short median overall survival (OS) of less than 2 years.[2]

Immunotherapy involving the application of multiple manipulation modes to a patient's immune system to recognize, tract, and destroy malignancies has recently altered the treatment landscape of oncology dramatically. Prominent in these approaches are checkpoint inhibitors, vaccines, and chimeric antigen receptor (CAR) T cells, which have been approved in more than 10 cancer indications by the US Food and Drug Administration (FDA).[3] These remarkable treatment outcomes have inspired novel research investigations into glioma immunotherapy. However, recent results from clinical trials have yet not demonstrated major improvements in the prognosis of patients with glioma. Some major reasons for these failures include genetic and antigenic heterogeneity, a paucity or absence of glioma-infiltrating lymphocytes, and the highly immunosuppressive tumor microenvironment (TME).[4] Besides, multiple other factors such as the physical and psychological characteristics of patients and routine treatment modalities are often neglected when designing immunotherapeutic approaches and evaluating clinical data.

The aim of this review was to identify how current treatments and patient-associated psy-

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chophysiological factors impact the effectiveness of immunotherapy, in order to facilitate the development of better strategies to advance this therapeutic modality in patients with glioma.

APPROACHES OF GLIOMA IMMUNOTHERAPY

Checkpoint inhibitors

Immune checkpoints play a major role in regulating the balance of stimulatory and inhibitory pathways that physiologically optimize immune responses and prevent immune overactivation.[5] Failed immune checkpoint signaling inhibits immune responses, which enhances the immune tolerance of cancers. Inhibitory immune pathways involving cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein (PD-1) and its ligand (PD-L1) have been identified as the main effectors participating in antitumor response inhibition.[6] Moreover, other inhibitory and stimulatory immune checkpoints exist, including T-cell immunoglobulin and mucin-domain-containing 3 (Tim-3), indoleamine 2,3-dioxygenase, T-cell immunoreceptor with Ig, ITIM domains, 4-1BB, and OX40 (also known as CD134).[7-10]

CTLA-4 expressed on T cells outcompetes its coreceptor CD28 by binding CD80/CD86 with higher affinity to impede the CD28 T-cell stimulatory pathway.[11] Anti-CTLA-4 blocking antibodies, including ipilimumab and tremelimumab, have been demonstrated to prevent the interaction between CD80/CD86 and CTLA-4, which results in stronger priming T cells, a more robust T-cell cytotoxic effector function, and decreased infiltration and functional deficiency of $Foxp3^+$ regulatory T cells (Tregs) at tumor sites.[12-15]

PD-1 is expressed more broadly than CTLA-4 in T cells in the TME,[10] and it mainly binds to its PD-L1 ligand, the expression of which is also up-regulated in glioma cells, tumor-associated macrophages (TAMs), microglia, Tregs, and myeloid-derived suppressor cells (MDSCs),[16-18] which leads to suppression of the function and proliferation of effector T cells, reduction of the production of proinflammatory cytokines such as interferon-γ (IFN-γ), interleukin-2 (IL-2) and IL-10, and augmentation of the activity and recruitment of Tregs to the tumor.[19-21] Blockade of interactions using the anti-PD-1 antibodies nivolumab and pembrolizumab or the PD-L1 inhibitors atezolizumab and durvalumab serves to enhance the population of cytotoxic T lymphocytes (CTLs), which augments the antitumor immune response and leads to tumor rejection.

Therapeutic vaccination

Antitumor vaccination approaches are a form of active immunotherapy involving vaccination with an antigenic target to activate a host immune response by augmenting the recruitment of antigen-specific effector T cells to the tumor.[22]

The foundation of peptide vaccines for glioma is based on selecting tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs) as immunogenic epitopes, which are typically linked with carrier proteins to enhance immunogenicity and are presented to antigen-presenting cells (APCs). TSAs are often the products of specific mutations and exclusively expressed on glioma cells, such as EGFRvIII and IDH-1 (R321H), and targeting them can reduce the risk of 'ontarget, offtumor' toxicities.[23,24] TAAs are more common, and they are native proteins shared by a large proportion of patients and also expressed at low levels in normal tissues, including IL-13Rα2, EphA2, gp100, and survivin.[25,26] Furthermore, multipeptide vaccines targeting various tumor antigens have been developed. This strategy can overcome limitations associated with several peptide vaccines being restricted to the HLA-A 02 haplotype, and targeting a single tumor antigen can lead to immune escape of tumor cells by the loss of antigenicity.[27,28]

Cell-based vaccines mainly consist of dendritic cells (DCs) that are highly potent APCs. DCs function to internalize, process, and present antigens to naïve T cells in the context of MHC I and II, which then triggers antigen-specific $CD8^+$ and $CD4^+$ lymphocyte responses. In contrast to preparing peptide vaccines, DCs can be expanded ex vivo and loaded with specific antigens or whole-glioma cell lysates, for subsequent reimplantation back into cancer patients to facilitate antitumor T-cell responses.[29] DC vaccines are currently used extensively in experimental treatments for glioma.[30-32]

CAR T-cell therapy

CAR T cells are engineered to connect an extracellular antigen-recognition domain to the intracellular signaling domain derived from the TCR ζ (CD3ζ) chain and costimulatory molecules (e.g., CD28 and CD137), which permits T cells to target the specific tumor surface antigen with high affinity and subsequently allows for T-cell activation and cytotoxic function.[33] The antigen-recognition domain is typically designed specifically for TAAs, and moreover the ectodomain is independent of MHC exposure that accommodates infinite antigenic diversity and overcomes the mechanism of immune evasion by MHC down-regulation.[34] CARs have been constructed to target EGFR, EGFRvIII, HER2, EphA2, and IL13Rα2 to create monovalent, bivalent, or trivalent T-cell products for treating glioma.[35-40]

INFLUENCES OF CURRENT TREATMENTS IN GLIOMA IMMUNOTHERAPY

Surgery

Surgery remains the mainstay treatment for glioma, the aim of which is to safely and maximally resect a tumor to achieve long-term disease control. Tumor resection is associated with increased OS time of patients with either lower-grade or grade IV glioma.[41-43] However, this clinical benefit depends on balancing the degree of cytoreduction with neurological morbidity. In some cases, the risk of neurological deficit due to a glioma being located in deep regions or eloquent areas of the brain makes it difficult to remove completely even when intraoperative monitoring techniques are applied.

A phase-III trial of newly diagnosed, EGFRvIII-expressing GBM found no significant difference in OS between patients with minimal residual disease receiving rindopepimut (a vaccine targeting EGFRvIII) and controls (median OS: 20.1 vs. 20.0 months), whereas a potential long-term survival benefit was found in exploratory analyses of a subset of patients with significant residual disease (2-year survival rate: 30% vs. 19%).[44] These findings might lead to the view that targeted immunity is more beneficial in patients with a larger residual tumor expressing the target antigen than when the tumor is completely resected.

Radiotherapy

Radiotherapy is a crucial component of glioma treatment that provides a directly cytotoxic antineoplastic effect and prognostic benefit when used alone or in combination with chemotherapy. Recent results have shown that this regimen may determine the immunogenic nature of glioma cells and influence the interface with the immune cells and the consequences of antitumor immunotherapies.

There is considerable evidence that ionizing radiation can induce immunological changes within the TME, including increasing the release of more TAAs or neoantigens for immune recognition, up-regulation of molecules (e.g., MHC I, CD95, and NKGD2) on tumor cells to facilitate the presentation of tumor antigen to CTLs, and increasing the infiltration and priming of tumor-specific T cells.[45,46] Radiation also increases the production of proinflammatory cytokines (e.g., IFN-γ) and chemokines (e.g., CXCL9, CXCL10, CXCL11, and CXCL16) to recruit cytotoxic T cells, induces the immunogenic cell death process by releasing damage-associated molecular patterns, and disrupts the blood–brain barrier to allow DCs as well as other immune cells to access the tumor site.[47-49] These effects of radiotherapy can augment the innate and adaptive immune response against a tumor. Accordingly, in two independent syngeneic murine glioma models, a subtherapeutic dose of local radiotherapy in combination with NKG2D-based CAR T-cell treatment showed synergistic efficacy by promoting the migration of CAR T cells to the TME and increased effector functions.[50] Moreover, it was found that radiation can up-regulate the expression of PD-L1 in glioma, which would help immune evasion by tumor cells,[51,52] which leads to the promising perspective of combining radiotherapy and checkpoint inhibitors. In a murine model with intracranial gliomas, anti-PD-1 blockade and stereotactic radiation produced long-term survival and increased the ratio of effector T cells to Tregs in the TME.[53] Combining radiotherapy and 4-1BB activation (stimulating $CD8^+$ T-cell proliferation), which is an inhibitor of another checkpoint CTLA-4, also significantly improved the OS of glioma-bearing mice and increased the number of $CD4^+$ and $CD8^+$ T cells in the tumors.[54] These findings indicate that the potentially beneficial immune-stimulating properties of radiotherapy can tip the balance from an immunosuppressive tumor milieu to an immunoactive one.

Modeling studies suggest that delivering ionizing radiation to malignant glioma within a localized region of the brain also results in substantial exposure to circulating lymphocytes due to the large blood flow in the brain and the long treatment duration.[55] A retrospective study of partial brain radiotherapy without concurrent chemotherapy for GBM found a steady decline of CD4 lymphocytes each week during the treatment course.[56] The same result was obtained in a murine model, where partial brain radiation without systemic therapy caused depletion of circulating lymphocytes, as well as depletion in nonirradiated distant lymph nodes.[57] Furthermore, it was found that cranial radiotherapy could substantially add to the lymphopenia induced by TMZ chemotherapy (discussed below) and that the low CD4 counts did not significantly recover over a long-term follow-up.[55] These data identify radiotherapy as an important contributing cause of lymphodepletion and a potentially actionable iatrogenic suppressor of the lymphocyte-mediated immune response. The ideal radiotherapy protocol for generating an immune effect with a reduced impact on lymphopenia remains unclear. Previous preclinical and clinical findings support that applying radiation with a short course, high daily dose, and hypofractionation may be effective without reducing the probability of success of immunotherapy for glioma,[58] but this needs to be investigated further.

Chemotherapy

While TMZ is the most commonly used agent in glioma chemotherapy, a malignancy will always acquire resistance to this regime and so tumor recurrence is inevitable. Previous stud-

ies have demonstrated that this chemotherapeutic agent could exert immunostimulatory effects by changing host immunity and the TME in both positive and negative ways.[59]

The systemic administration of TMZ contributes to immune suppression, including myelosuppression and lymphodepletion over a long period, and the proliferating immune cells such as activated T cells can also undergo apoptosis under the cytotoxic stress induced by TMZ.[60,61] The immunosuppressive effects of TMZ chemotherapy are probably stronger in malignant glioma patients, whose peripheral immune system is also profoundly affected by the tumor, which will reduce the effectiveness of immunotherapies.[55,60] However, clinical studies found that TMZ treatment led to up-regulation of chemoresistance-associated peptides such as WT-1, gp-100, and MAGE-A3, which might help the immune system to exert stronger antitumor effects in vaccination therapies that involve generating fusion cells from DCs and glioma cells, and induced an increased tumor mutational load, which suggested that checkpoint inhibitors have great promise in such tumors with hypermutation.[62,63]

Attempts are currently being made to manipulate the dose, mode of delivery, and timing of chemotherapy administration so as to improve the efficacy of different immunotherapeutic approaches. This idea is supported by preclinical evidence that treating mice locally with chemotherapy increased the infiltration of tumor-associated DCs and the clonal expansion of antigen-specific T effector cells, while the combination of anti-PD-1 and local chemotherapy facilitated an antitumor immune response and improved survival in GBM, whereas anti-PD-1 antitumor immunity or provoked immunological memory would be reversed by systemic chemotherapy.[64,65] Moreover, different regimens with intense doses or the metronomic or standard dose of systemic TMZ chemotherapy might not exert the same effects on antitumor immune response despite them providing similar clinical efficacy. In murine glioma models, the standard TMZ regimen reduced both $CD4^+$ and $CD8^+$ T cells compared with metronomic treatment, and resulted in the exhaustion of tumor-infiltrating lymphocytes and reversal of the survival advantage in anti-PD-1 therapy, while metronomic TMZ preserved the activity of CTLs and the survival benefit.[59] Another model study found that dose-intensified TMZ pretreatment dramatically enhanced the proliferation of CAR T cells and their persistence in the circulation compared with treating with CAR T cells alone or the standard of care comprising TMZ plus CAR T cells, and that the combination of dose-intensified TMZ and CAR T-cell therapy induced complete regression of 21-day established GBM, which prompted a phase-I trial of newly diagnosed GBM patients involving dose-intensified TMZ as a preconditioning regimen prior to treatment with CAR T cells.[66] The findings of these studies also highlight the potential of administering immunotherapy after TMZ to generate stronger immune responses, since TMZ-induced lymphodepletion can ablate immunosuppressive cells, reset the host immune system, and then allow for the expansion and persistence of T cells in the TME. This hypothesis was supported by a clinical trial in which dose-intensified TMZ resulted in GBM patients exhibiting higher grade lymphopenia than those receiving the standard dose, and produced increased antigen-specific immune responses following EGFRvIII-targeted vaccination.[67] Accordingly, in order to achieve greater clinical efficacy, optimal parameters such as for the dose of TMZ and timing schemes of combination therapy need to be established in further clinical studies.

Antiangiogenesis

Angiogenesis is a hallmark of malignant glioma that represents an important therapeutic target. Antiangiogenic strategies have mainly focused on the VEGF signaling pathway, which not only drives tumor angiogenesis and vascular permeability but also harms the function of effector T cells and the maturation and antigen presentation of DCs.[68-70] Moreover, vessel normalization by antiangiogenesis also allows the recruitment of adaptive immune cells that may help to enhance the antitumor response.[71] Preclinical studies of glioma have shown that an anti-VEGF therapy called VEGF-Trap (a VEGF receptor fusion protein conjugated to a human IgG Fc region) can promote a more-mature phenotype of DCs with increased expression of the costimulatory molecules B7-1, B7-2, and MHC II in the brain, while reducing the levels of the exhaustion markers PD-1 and Tim-3 on brain-infiltrating CD8 T cells.[72] Blockage of VEGF with VEGF-Trap and anti-Ang-2 (AMG386) therapy followed by a checkpoint inhibitor improved survival by altering the TME nourished with $CD8^+$ CTLs and reduced immunosuppressive MDSCs and Tregs.[68]

Bevacizumab is a monoclonal antibody that blocks the effect of VEGF, and it was approved by the FDA in 2009 as a second-line treatment for recurrent GBM and has been studied as a monotherapy or in combination therapy in several clinical trials of malignant glioma.[73-75] Despite no significant OS benefit being demonstrated, most neuro-oncologists continue to believe that there is a role for bevacizumab. Continuous bevacizumab administration has been demonstrated to restore the immune-supportive glioma microenvironment by decreasing the expression of PD-1/PD-L1, suppressing the infiltration of TAMs and Tregs, and increasing CTL infiltration.[76] Bevacizumab can also decrease the number of peripheral Tregs that might modulate the TME.[77] These results suggest that bevacizumab plus immunotherapy represents a ratio-

nal combination therapy. Administering the combination of ipilimumab and bevacizumab was found to elicit a partial response in 31% of patients with GBM.[78] However, a more-recent exploratory study revealed that prior IMA950 peptide vaccination did not alter the subsequent response to bevacizumab in relapsing patients with high-grade glioma.[79] Therefore, the administration sequence of antiangiogenesis and immunotherapeutic interventions should be optimized in order to integrate their synergistic effects against glioma, while it is also important to identify the immunotherapy strategy that best fits bevacizumab treatment.

Tumor-treating fields

TTFields has become the fourth modality in cancer treatment, which involves delivering low-intensity, intermediate-frequency alternating electric fields to the tumor. The TTFields therapy was recently approved by the FDA for use in newly diagnosed GBM, based on a phase-III trial finding that the median OS improved from 16.0 months in the TMZ-only group to 20.9 months in the TTFields-plus-TMZ group.[80] The mechanisms of action of TTFields include mitotic arrest/delay, suppression of proliferation and invasion, disruption of DNA damage repair, and induction of apoptosis and immunogenic cell death.[81,82] Its tumor-killing effect can also be enhanced by regulating genes related to the cell cycle and cell death in glioma.[83] Immunogenic cell death can activate robust innate immunity such as by activating the STING pathway and releasing proinflammatory cytokines and chemokines.[84] There is also evidence that TTFields promotes the eradication of cancer cells by DCs and DC maturation in vitro and the recruitment of immune cells in vivo.[85] Thus, TTFields appears to strengthen the antitumor response by altering the immune system in the inflammatory environment. Indeed, combining TTFields with anti-PD-1 therapy was found to enhance antitumor effects, by increasing the percentage of tumor-infiltrating lymphocytes that led to significant tumor regression in lung and colon cancer animal models.[85] These findings provide a practical basis for applying glioma immunotherapy after TTFields to potentiate the immune system response against a tumor.

Corticosteroids

Corticosteroids (mainly dexamethasone) are commonly used perioperatively in the treatment of patients to reduce brain edema and suppress adverse effects related to radiotherapy, but they can also compromise the survival of glioma patients.[86] Previous studies found that corticosteroid administration was an independent risk factor for a poor prognosis in three large independent cohorts of GBM.[86] The mechanism has not been fully elucidated, but it is proposed that corticosteroids can worsen systemic immune suppression and the immunosuppressive TME, which may contribute to the failure of current treatments for glioma. Model studies found that corticosteroid therapy resulted in severe and persistent reductions in peripheral $CD4^+$ and $CD8^+$ T cells, while dexamethasone upregulated CTLA-4 expression in $CD4^+$ and $CD8^+$ T cells and blocked naïve T-cell proliferation and differentiation by attenuating the CD28 costimulatory pathway.[87,88] Consistently, a recent phase-Ib GBM trial showed that patients receiving dexamethasone during vaccine priming failed to generate a de novo immune response against multiple predicted neoantigens, and no increase in infiltrating $CD8^+$ T cells was detected, whereas a robust antitumor response was observed in patients who did not receive dexamethasone.[89] It is particularly interesting that some study findings have led to the novel viewpoints that corticosteroids do not reverse the benefits conferred by anti-PD-1 therapy and low-dose dexamethasone does not diminish the antitumor activity of CAR T cells in glioma models,[88,90] which indicates that further clinical data are required to verify the feasibility. In any case, the prudent and restricted use of corticosteroids in malignant glioma should be advocated, especially when patients receive immunotherapy.

EFFECTS OF PHYSICAL AND PSYCHOLOGICAL CONDITIONS ON GLIOMA IMMUNOTHERAPY

Aging

Age is a strong predictive factor for the occurrence of glioma and an independent prognostic factor for patients.[91-93] It has been found that aging can induce somatic mutations that increase the incidence and malignancy of glioma, and recent studies have also highlighted the potential importance of aging-associated immunosenescence.[94-96] Also, the altered immune status of aged patients may compromise their anticancer immunity due to small numbers of naïve T cells, exhaustion of potentially tumor-specific memory T cells, and larger numbers of suppressive cells.[97] A retrospective analysis predicted that the outcomes of patients with GBM receiving DC vaccine adjuvant therapy are worse in the elderly.[98] However, there is some evidence that responses in other cancers including melanoma and non-small-cell lung cancer to anti-PD-1/PD-L1 are larger in older patients than in younger cases.[99,100] It is therefore difficult to conclude the impact of age on antiglioma immunotherapy, and so other factors such as the type of immunotherapy, the ratio of $CD8^+$ cells to Tregs, and the expression level of checkpoint molecules should also be considered when designing clinical trials focusing on the effects of age.

Sex

Sex-related differences in the susceptibility to cancers are widely reported. Consistently, data from epidemiological investigations have shown higher glioma burdens as well as lower survival rates in males relative to females.[101,102] In addition, sex-specific molecular subtypes of GBM and different sensitivities to standard therapy have also been found.[103] The main causes are thought to be genetic, environmental, and hormonal factors, which are possibly attributable to their effects on the immune system. It has been demonstrated that immune components of both innate and adaptive immunity are regulated differently in females and males,[104] which may also contribute to sex differences in the responses to cancer immunotherapy. For example, high levels of estrogens up-regulate PD-1 on Tregs and effective T cells, suggesting higher efficacy of anti-PD-L1 treatment in female patients with cancer.[105] Future studies should investigate how sex affects immune function, since sex-specific changes represent an opportunity to optimize individualized treatments of malignant glioma.

Obesity

Obesity is a major risk factor for certain malignancies and promotes tumor progression, possibly due to generalized immune system dysfunction including increased immune aging and PD-1-mediated T-cell dysfunction.[106] However, this dysfunction in obesity remarkably left tumors markedly more responsive to checkpoint blockade, which has been found in both tumor-bearing mice and clinical cancer patients.[106] Thus, obesity can be regarded as a potential mediator of immune dysfunction that can be reversed by PD-1 checkpoint blockade so as to increase treatment efficacy. However, the efficacy of antitumor immunotherapy might be reduced by elevated leptin, based on results seen in preclinical studies on mice with diet-induced obesity.[107] These data indicate the potential of targeting leptin or losing weight to enhance the effects of immunotherapy in obese patients with malignant glioma.

Stress

Cancer patients are subjected to many different types of stress, including the acute stress of getting the disease diagnosis, and especially the chronic stress of receiving long-term treatment, withstanding financial pressures, and worrying about tumor progression. These stresses can induce physiological changes mediated by interactions between the nervous, endocrine, and immune systems. Epidemiological and clinical findings have demonstrated that exposure to chronic stress can promote tumor progression mainly via immunosuppressive effects.[108,109] Studies using diverse cancer models found that immunosuppression caused by stress occurred both in the central and peripheral nervous systems, and that the dysregulation of immune function could be influenced by stress in several ways. Chronic stress can increase the polarization of protumor M2-like TAMs and the density of MDSCs in the TME, induce the production of hormones such as corticosteroids and its downstream effector TSC22D3 to prevent the maturation of DCs and impair its capacity of antigen presentation, impede the priming of $CD8^+$ T cells along with an elevated expression of PD-1, and decrease the number of tumor-infiltrating CTLs.[110-113] It is plausible that these effects of chronic stress perturb therapeutic responses to antitumor vaccination and PD-1-targeted immunotherapy. Stress has also been found to modulate the gut microbiome, which could affect the efficacy of cancer immunotherapy, as discussed in the next section.[114] In summary, providing psychological support to cancer patients should form an important part of their management. Intervention methods to support the immune system may range from providing psychological guidance and an enriching environment, to blocking stress-induced hormones and administering antidepressants.

Gut microbiome

The human gut microbiome comprises at least 100 trillion microorganisms that influence physiological functions of the host organism in both healthy and disease conditions, including cancer.[115,116] There is emerging evidence that imbalances in the gut microbiota can potentiate tumor development by modulating the metabolism, inflammation, and adaptive immunity.[115,117] Dysbiosis has also been shown to affect cancer responses to immunotherapy, with several recent studies finding that the gut microbiota regulates the efficacy of anticheckpoint cancer therapy, since the diversity and composition of the gut microbiome differed significantly between respond-

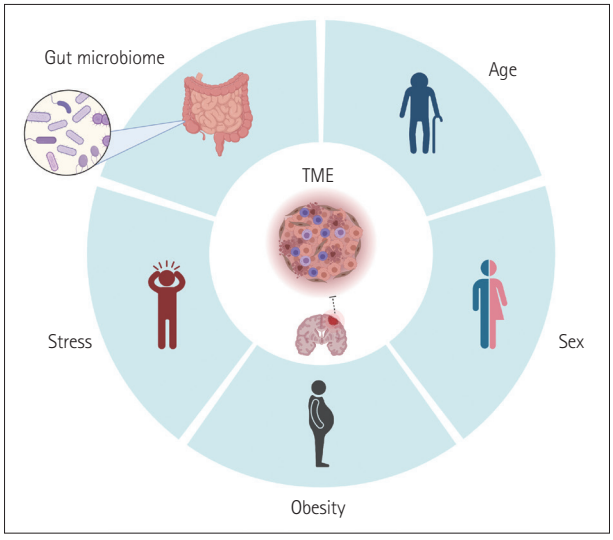

Fig. 1. Multiple factors potentially impact treatment responses to glioma immunotherapy. TME, tumor microenviroment.

ers and nonresponders. In mice and patients, *Bacteroides fragilis* enhanced the antitumor immunity of CTLA-4 blockade, and an abundance of members of the *Bifidobacterium* genus or *Ruminococcaceae* family, or of *Akkermansia muciniphila* increased the efficacy of anti-PD-L1 in treating melanoma.[118-121] Furthermore, the oral administration of beneficial fecal microbiota obtained from cancer patients who responded to checkpoint inhibitors significantly improved tumor control in nonresponders.[118-121] These results suggest that changes in the gut microbiota composition including in the abundance of individual species can modulate responses to immunotherapies in glioma, which potentially makes it important to identify specific gut microbes in responding patients.[122] However, caution is necessary when using antibiotics in patients receiving immunotherapy.

Conclusions

In the era of the standard of care, most patients with malignant glioma are treated using a routine procedure that is of little benefit to OS. Immunotherapy holds the promise of antiglioma efficacy due to surging numbers of FDA approvals for several malignancies. Clinical and preclinical studies have revealed that there remain great challenges to achieving long-term tumor control in glioma immunotherapy. Systemic and intratumoral changes have been explored with the aim of identifying novel therapeutic targets or biomarkers that would enable the further selection and stratification of patients for the application of precision treatments. There is considerable evidence that in addition to the biological characteristics of tumors influencing the antineoplastic immunity and efficacy of different immunotherapy approaches, factors related to current therapeutic regimes (Fig. 1) and the physical and psy-

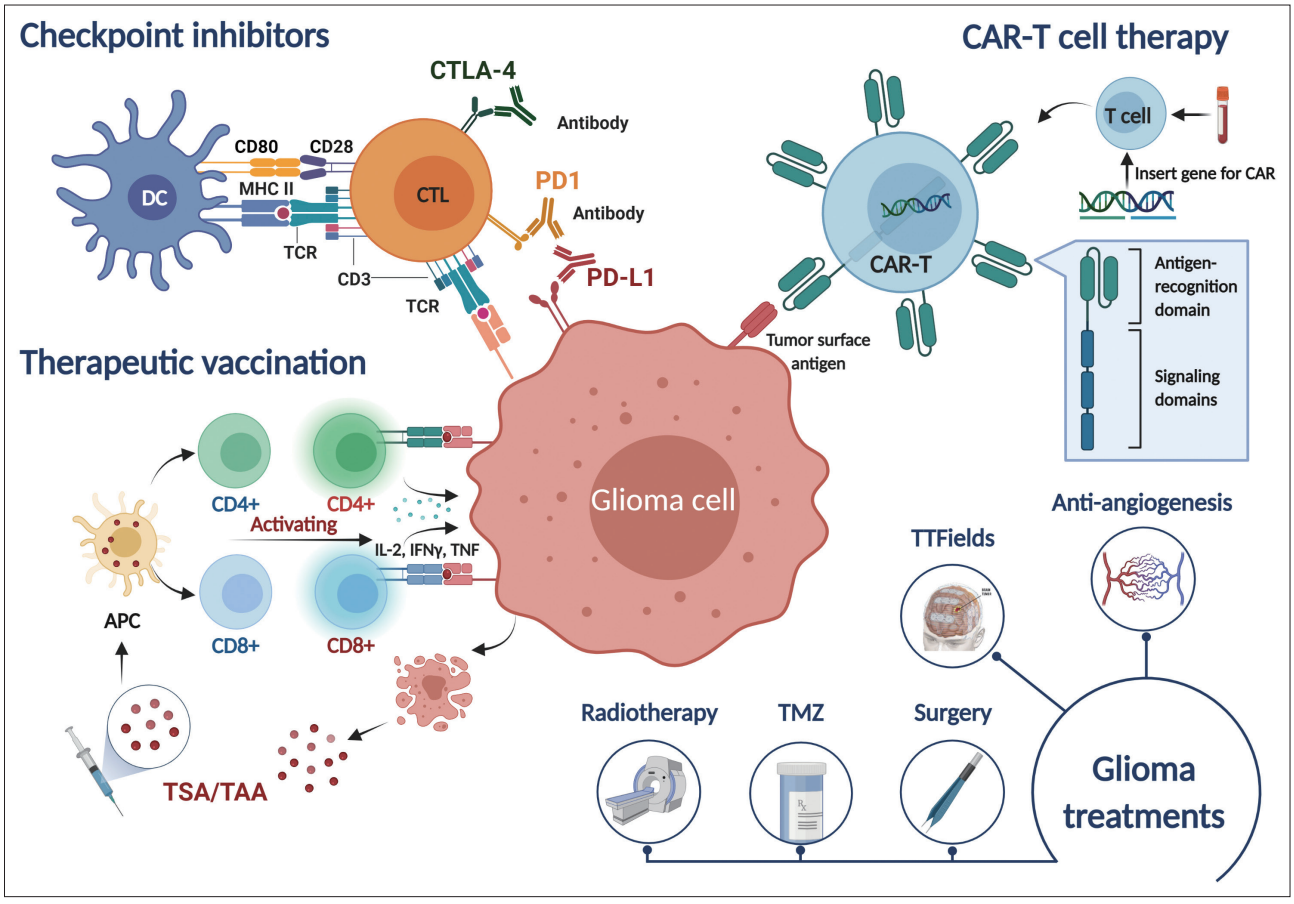

Fig. 2. Common immunotherapeutic modalities and current standard treatments for glioma. Immune checkpoint inhibitors, led by inhibitors of PD-1, PD-L1, and CTLA-4, can block the interaction between immunosuppressive checkpoints and host immune cells, thereby enhancing the antitumor function of CTLs. CAR T cells encode a synthetic T-cell receptor that has high affinity to a specific antigen on the tumor cell surface. Therapeutic vaccination with TAAs/TSAs can induce tumor-specific immune responses by CTLs. Current standard treatments including surgery, radiotherapy, temozolomide chemotherapy, TTFields, and antiangiogenesis therapy can exert detrimental or favorable effects on these immunotherapeutic strategies. APC, antigen-presenting cell; CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; PD-1, programmed cell death protein; PD-L1, programmed cell death protein ligand; TAA, tumor-associated antigen; TCR, T-cell receptor; TMZ, temozolomide; TNF, tumor necrosis factor; TSA, tumor-specific antigen; TTFields, tumor-treating fields.

chological conditions (Fig. 2) of individual subjects also play pivotal roles in the immune profile of glioma and the outcomes of immunotherapy-based strategies. All of these factors highlight the importance of applying comprehensive management to each glioma patient, which needs to integrate traits of the tumor, characteristics of the patient, and immunomodulation of received routine treatments in order to identify and apply the optimal therapeutic scheme. Management strategies will be improved by future developments in artificial intelligence involving machine learning to overcome the heterogeneity of biological and clinical data in order to extract meaningful information for use in personalized treatment decision-making.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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