Review

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# CAR-T-cell therapy in meningioma: current investigations, advancements and insight into future directions

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**Abstract**

Meningiomas, the most common tumors of the central nervous system (CNS), present significant challenges in treatment, particularly for atypical and anaplastic subtypes where standard therapies often fall short of therapeutic expectations. Chimeric antigen receptor (CAR) T-cell therapy, a groundbreaking immunotherapy approach, has demonstrated great success in hematological malignancies but faces obstacles in solid tumors, including CNS tumors like glioblastomas. This article provides a comprehensive review of the efficacy of CAR-T therapy in meningiomas, highlighting the tumor's immunogenic potential and the challenges associated with applying this therapy in clinical practice. Through an extensive literature review, the study explores potential antigens for CAR-T targeting in meningiomas, shedding light on the tumor-immune microenvironment interactions. Challenges such as tumor heterogeneity, blood-brain barrier penetration, off-target effects, and tumor recurrence are discussed, alongside potential strategies to overcome these obstacles. The study also investigates recent advancements in CAR-T therapy, including the identification of novel target antigens and the development of engineering approaches to enhance therapeutic efficacy. Furthermore, the article highlights the importance of ongoing research efforts in exploring the tumor-immune dynamics in meningiomas and underscores the urgent need for clinical trials to validate the safety and efficacy of CAR-T therapy in this context. By addressing these challenges, CAR-T therapy holds the promise of revolutionizing meningioma treatment, offering new hope for patients suffering from this disease.

**Keywords:** CAR-T-cell, meningioma, T-cell, immunity

## Introduction

Meningiomas are the most common tumors of the central nervous system (CNS), accounting for approximately one-third of all primary intracranial adult tumors. However, they are rare in children and adolescents[1]. Meningiomas are more prevalent in females, with a female-to-male ratio of 2-4:1. The annual incidence of meningiomas increases with age[2] and is highest among Caucasian populations. Interestingly, being of African American descent is an independent risk factor for tumor relapse[3]. The majority of meningiomas (80–90%) are benign and are typically cured by either surgery or radiotherapy. Conversely, the less common atypical and anaplastic meningioma subtypes are malignant, and the traditional treatment modalities of surgery, radiotherapy, or chemotherapy are often ineffective[4]. Hence, there is an urgent need to explore new strategies to address the limitations in the treatment of these aggressive meningioma variants.

### HIGHLIGHTS

- Chimeric antigen receptor (CAR) T-cell therapy, a groundbreaking immunotherapy modality, has shown great success in hematological malignancies but faces some challenges in solid tumors, including CNS tumors like glioblastomas.
- This article provides a comprehensive review of the efficacy of CAR-T therapy in meningiomas, highlighting the tumor's immunogenic potential and the challenges associated with applying CAR-T therapy in clinical practice.
- Through a comprehensive literature review, potential antigens for CAR-T targeting in meningiomas are explored, shedding light on the tumor-immune microenvironment interactions.

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Chimeric antigen receptor (CAR) T-cell therapy is a revolutionary form of cellular immunotherapy that involves extracting T cells from a patient's blood, engineering these T cells to express synthetic antigen receptors, and then infusing the modified T cells to target tumor antigens[5]. CAR-T-cell therapy has achieved remarkable success in the treatment of hematological malignancies[6]. However, the application of CAR-T therapy in solid tumors, including intracranial tumors, has faced unique challenges. The success of CAR-T-cell therapy in solid tumors, such as mesothelioma[7], breast[8], prostate[9], and ovarian cancers[10], has spurred interest in applying this technology to solid tumors, including meningioma. The hostile tumor microenvironment and the heterogeneous antigen expression patterns of solid tumors represent significant obstacles for effective CAR-T therapy[11]. While numerous clinical trials have been conducted to assess the efficacy of CAR-T-cell therapy in the treatment of glioblastoma multiforme, the benefits of this modality have been limited[12]. Further challenges faced by CAR-T therapy in solid tumors are the dense structure of the tumors, making the infiltration and penetration an obstacle[13]. Various engineering challenges were also found as obstacles in solid tumors, as designing T cells with optimized structures for different tumors is a time and energy-consuming task[14]. Furthermore, safety was a concern where potential off-targets by the CAR-T therapy may constitute healthy tissues and get damaged, leading to adverse and unwanted effects[15].

Our study aims to investigate the feasibility and efficacy of CAR-T-cell therapy in the treatment of meningiomas. Through a comprehensive review of the literature, we explore the potential antigens for CAR-T-cell targeting in meningiomas and the challenges associated with implementing this therapy in meningioma patients. By shedding light on the therapeutic potential of CAR-T-cell therapy in meningiomas, our study contributes to the body of literature aimed at enhancing the management of these challenging tumors.

## Methods

A comprehensive literature search was conducted on PubMed/MEDLINE using the MeSH keywords "CAR T cell", "meningioma", "chimeric antigen receptor", and "t-cell". All relevant English-language studies, including original articles, case reports, clinical trials, systematic reviews, and meta-analyses, were included in our review. However, gray literature, posters, abstracts, non-peer-reviewed articles, non-English articles, and articles without full-text availability were excluded from the analysis. The efficacy and challenges of CAR-T-cell therapy in meningiomas were evaluated through a qualitative synthesis of relevant studies, categorized by focus. Key information on mechanisms, target antigens, outcomes, and challenges was analyzed to identify common themes and gaps. This provided a comprehensive overview of the current state of CAR-T-cell therapy in meningiomas and highlighted areas needing further research.

### *T-cell profile of meningioma*

For patients with metastatic cancer, tumor immunotherapy is a potentially effective treatment approach. T cells have been shown to be essential for cancer immunotherapy, as they are important mediators of anti-tumor action, specifically identifying and responding to antigens expressed by tumors. However, T cells do not combat cancer as effectively as one might anticipate. This is partially due to the fact that T cells eventually reach a dysfunctional or fatigued state, which is distinguished from functioning effector or memory T cells by the prolonged expression of inhibitory receptors and a different transcriptional state.

Tumors that grow out of control are often caused by this T-cell malfunction. T-cell dysfunction has been extensively studied in a variety of clinical and experimental contexts. Despite this, progress has been made in understanding the molecular definition of T-cell malfunction and its underlying causes. This review will cover the development of prospective immunotherapies to block the processes of tumor-induced T-cell dysfunction, along with current developments in the molecular mechanisms affecting the TME and causing T-cell dysfunction. Gaining further insight into these fundamental processes could result in the development of fresh approaches to enhance the clinical outcomes for cancer patients[16].

Meningiomas are the most common primary cerebral tumors. While surgery and/or radiation therapy can manage the majority of symptomatic cases, a significant proportion of patients have an unfavorable clinical course, necessitating the need for additional therapeutic alternatives. Meningiomas may be an accessible target for immunotherapy since they are frequently perfused by dural branches of the external carotid artery, which are situated outside the blood-brain barrier. However, it is unknown how many naturally occurring tumor antigens are present in meningioma.

This study offers a T-cell antigen atlas for meningioma using detailed LC-MS/MS profiling of the naturally occurring immunopeptidome. A comprehensive immunopeptidome data collection of normal tissues was used to inform the comparative technique that was used to determine candidate target antigens. The authors describe HLA class I and II meningioma-exclusive antigens and further characterize the immunogenicity of top-ranking targets through in-vitro T-cell priming experiments. This atlas of meningioma T-cell antigens will be made freely available to support future research on potential meningioma immunotherapy strategies[17].

According to the WHO categorization, there are three distinct grades of malignancy in meningiomas. Radiation therapy is typically reserved for certain instances with unfavorable clinical behavior or higher-grade histological and molecular characteristics. Surgery remains the cornerstone of treatment for symptomatic meningiomas. Other systemic therapy approaches are still in the experimental stage, despite recent progress in the molecular understanding of meningiomas and the introduction of contemporary diagnostic techniques like next-generation sequencing and DNA methylation profiling. These methods have only shown limited success thus far, leading to the lack of a clear standard of care. Effective therapeutic alternatives are still desperately needed for meningiomas that are resistant to radiation and surgery. T-cell immunotherapy has shown promise in treating other tumor types, suggesting that meningiomas may also benefit from this approach. Moreover, meningiomas are supplied by vascular branches of the external carotid artery, which are more accessible to immune cell infiltration as they are not blocked by the blood-brain barrier. However, little is known about the landscape of relevant T-cell antigens in meningiomas that could serve as the basis for antigen-specific immunotherapy[17].

One of the most prevalent adult CNS neoplasms is meningiomas, which are brain tumors that develop from the meninges around the brain and spinal cord. Despite being slow-growing, non-malignant grade I tumors according to the WHO, 80% of meningiomas can nevertheless be harmful if they have a mass effect on nearby structures. Surgical excision of the entire tumor can often result in favorable outcomes for those WHO grade I tumors. On the other hand, WHO classifications II and III of atypical meningiomas have the potential to be more catastrophic. Patients with grade II and grade III tumors have 5-year survival rates of 78.5% and 44%, respectively, and corresponding 10-year survival rates of 53.3% and 14.2%, despite receiving optimal management, which includes surgical excision and radiation therapy.

Meningiomas have complex interactions with the immune system that present significant challenges for effective treatment. The tumor microenvironment of meningiomas is often highly immunosuppressive, with the presence of various immunosuppressive factors and cells[18]. Additionally, the blood-brain barrier (BBB) surrounding meningiomas acts as a major obstacle, limiting the penetration and efficacy of many therapeutic agents, including immunotherapies[19].

The BBB is a highly selective barrier that tightly regulates the transport of molecules between the bloodstream and the CNS. This barrier plays a crucial role in maintaining homeostasis and protecting the delicate brain tissue[20]. However, in the context of meningiomas, the BBB can present a significant challenge for therapeutic interventions[19]. Meningiomas, unlike many other brain tumors, are not confined by the BBB, which allows peripheral immune cells to infiltrate the tumor microenvironment more readily. Nevertheless, the BBB can still limit the penetration of certain therapeutics, particularly large molecules like monoclonal antibodies, into the CNS. The restricted access of these therapeutic agents to the tumor site can hinder their ability to exert their intended anti-tumor effects[19].

This challenge posed by the BBB highlights the need for novel delivery strategies or the development of smaller, more BBB-permeable therapeutic agents to overcome this barrier and improve the efficacy of immunotherapies and other targeted treatments for meningiomas.

In addition to the barrier presented by the BBB, the tumor microenvironment of meningiomas can also be highly immunosuppressive, further complicating the treatment of these tumors. In meningiomas, a significant fraction of the cells in the tumor microenvironment are immune cells with CD45 + status. Despite the presence of immune cells, including natural killer (NK) cells, myeloid cells, and CD3 + T cells (predominantly CD8 + cells) in the meningioma microenvironment, the tumor actively suppresses the anti-tumor immune response[21]. One mechanism by which meningiomas create an immunosuppressive environment is through the recruitment of regulatory T cells (Tregs), which can inhibit the anti-tumor immune response and foster an immunosuppressive landscape.

Meningiomas also secrete immunosuppressive factors, such as transforming growth factor-beta (TGF-β), which can directly suppress the activity of effector immune cells, such as cytotoxic T cells and NK cells, further hindering the anti-tumor immune response[22]. Furthermore, meningiomas can upregulate the expression of immune checkpoint proteins, like programmed death-ligand 1 (PD-L1), which can induce an inhibitory signal that leads to T-cell exhaustion and the suppression of the anti-tumor immune response[23].

Numerous studies on non-CNS tumors, including melanoma, lung cancer, ovarian cancer, and colon cancer, have shown that the presence and distribution of infiltrating lymphocytes can play a significant role in predicting clinical outcomes. It has been proposed that the patterns and types of these infiltrating lymphocytes may serve as more potent prognostic markers than the pathological criteria for oncogene expression or tumor stage that were previously employed. For instance, long-term survival is frequently associated with a high ratio of regulatory T cells (Treg) to tumor-infiltrating CD8 + cells. On the other hand, rapidly expanding tumors can also have a strong T-cell response and antibody production, suggesting that an immunological response does not always translate into immune protection. The interaction between the immune system and tumors is complex, and the outcome cannot be predicted based solely on the size of the tumor.

These mechanisms employed by meningiomas to create an immunosuppressive microenvironment represent significant challenges in harnessing the immune system for effective anti-tumor responses. Overcoming this immunosuppressive environment is crucial for developing successful immunotherapeutic strategies against meningiomas.

Meningiomas can include varying amounts of T cells, B cells, plasma cells, and macrophages within their immune cell infiltrates. While the descriptive presence of these immune cells in meningiomas has been clearly defined, many of their properties remain unclear. One of the first steps towards understanding their significance in tumor biology is determining whether such cells exhibit fatigued phenotypes, have differentiated into activated effector cells, or demonstrate antigen experience. In the current work, we began elucidating the function of the immune cells that comprise the tumor parenchyma in meningiomas[21].

The analysis revealed that meningiomas contained populations of immune checkpoint marker-expressing cells, including PD-1 and Tim-3-positive T cells, regulatory T cells, and antigen-experienced CD4 + and CD8 + memory/effector T cells, all of which were suggestive of an exhausted immunological state. These phenotypes were significantly enriched compared to their frequency in the circulation. Moreover, there were distinct T-cell populations present within the tumor microenvironment that were not found in the matched peripheral blood samples[24].

The B cell populations identified were frequently from the post-germinal center, and were consistently present in the tumor microenvironment of meningiomas. Additionally, a specific, antigen-experienced effector T-cell population that was enriched in cells expressing hallmarks of an exhausted phenotype was consistently observed in these tumors[24].

The importance of the tumor microenvironment (TME) in the pathogenesis of various cancers has become increasingly apparent. However, the TME in meningiomas is poorly understood, and it is uncertain whether glial cells play a role in the development and behavior of these tumors. This scoping review examines the available data on the involvement of the brain parenchyma in the pathophysiology of meningiomas and investigates whether the literature supports tumor-brain crosstalk in meningiomas[25].

The most prevalent immune cell type found to infiltrate meningiomas was monocytes. Notably, a monocytic response was only observed at the tumor-brain interface in brain-invasive meningiomas. Substantial research has been conducted on the

production of cytokines and chemokines in meningiomas, with some of these factors creating autocrine loops within the cancer cells. However, how glial cells and cancer cells communicate paracrinally remains unexplored. In conclusion, the extent to which meningiomas trigger an immune response in the brain parenchyma is unknown. It is hypothesized that tumor-brain interaction may only be significant when invasive meningiomas cause damage to the pial-glial basement membrane[25].

Non-neoplastic inflammatory cells, primarily macrophages with minor proportions of T- and B-lymphocytes, plasma cells, and mast cells, can comprise up to 24% of all cells in meningiomas. There is evidence that the meningioma lymphocytic infiltration is antigen-experienced and may partially reflect underlying molecular changes. The relationship between meningioma tumor-infiltrating lymphocyte (TIL) density and WHO grade is inconclusive. It has been documented that atypical and anaplastic meningiomas express PD-L1 and have decreased CD4 + and CD8 + TIL density along with elevated FOXP3 + TILs. Conversely, other studies have shown elevated CD3 + TILs in meningioma grades above grade I. Despite these findings, few studies have examined TIL density in a large meningioma cohort to assess variations in TIL density according to meningioma histology and its potential predictive value. The purpose of this study was to determine whether the density of any of these TIL subgroups predicts recurrence and how the staining density of TILs for CD3, CD8, CD4, FOXP3, and PD-1 varies by meningioma histology[22].

The figure (Fig. 1) provides a comprehensive illustration of the key aspects discussed. Panel A shows the anatomical location of a meningioma situated in the meninges, pushing against the cerebral cortex. Panel B depicts the meningioma tumor microenvironment, illustrating the interaction between meningioma cells, CD45 + lymphocytes, and CAR-T cells, along with other cell types such as B cells, plasma cells, macrophages, and monocytes. The infiltration of CAR-T cells into the tumor site is also illustrated. Panel C highlights the known antigens that could potentially be used as targets for CAR-T-cell therapy, with an inset diagram showing a chimeric antigen receptor (CAR) interacting with a target antigen on a meningioma cell.

### *Current challenges and limitations*

Hematological cancers can now be effectively treated using chimeric antigen receptor T-cell (CAR-T) therapy. The FDA approved Novartis' Kymriah (CAR-T cells that target CD19) in August 2017, signaling the actual clinical introduction of CAR-T-cell therapy and positioning it as a promising technique for treating tumors. The Food and Drug Administration (FDA) authorized Yescarta, the second CAR-T-cell treatment in history, in October 2017. The introduction of these products has brought widespread attention to CAR-T-cell treatment.

Although CAR-T-cell therapy has shown great promise in the treatment of tumors, there are still several clinical challenges, including high rates of tumor recurrence, poor therapeutic efficacy in solid tumors, and cytokine release syndrome (CRS). Currently, there is a strong focus on addressing the toxicity and side effects of CAR-T therapy, leading to research into establishing better management strategies.

Advances in understanding the treatment and ongoing optimization of therapeutic regimens have helped to somewhat manage the toxicity and side effects of CAR-T therapy. This study aims to provide physicians and scientists with a foundational reference for managing CAR-T therapy in clinical practice and CAR-T therapy research, by analyzing the recent issues with the clinical application of CAR-T therapy and introducing corresponding strategies[26].

Selecting the appropriate antigen for CAR-T treatment is a major challenge, as the majority of antigens found in tumor cells are also present in healthy human cells[26]. This lack of tumor-specific antigen targets presents a significant obstacle in developing effective and safe CAR-T therapies.

Notwithstanding the ongoing advancements in CAR-T therapy, a number of issues with its underlying science and clinical use remain unresolved and require immediate attention. These include the several adverse effects associated with cytokine release syndrome (CRS) and the inadequate therapeutic efficacy in solid tumors. The ongoing advancements in site-specific genome editing and cell engineering, however, hold promise to increase the safety and efficacy of CAR-T therapy, potentially expanding its clinical use in the treatment of diverse tumor types[26].

The concept of creating a customized immune response to cancer has advanced from theory to practice within the past ten years. Using the patient's own immune cells, CAR-T-cell treatments have proved revolutionary for certain forms of aggressive leukemias and other blood malignancies. They have even been able to cure some patients whose cancer returned despite receiving numerous prior therapies. For most people, however, CAR-T cells do not yet result in long-term survival. Furthermore, it has been challenging to transition from treating blood malignancies to treating solid tumors like lung, colorectal, or pancreatic cancer. When immune cells target solid tumors, they encounter various obstacles, including competition from other cells for limited nutrients, an environment full of chemicals that might disarm or inhibit immune cells, and eventually a decreased capacity to kill other cells—a phenomenon commonly referred to as exhaustion[27].

The FDA has approved six CAR-T-cell treatments since 2017, all of which are used to treat blood malignancies[27]. This rapid regulatory approval highlights the transformative potential of this novel cancer therapy.

The first trial of CAR-T-cell therapy was published in 2010 by an NCI research team. They described a single patient with advanced lymphoma whose disease "underwent a dramatic regression" as a result of the treatment. When CAR-T-cell therapy was used to treat a patient with an advanced form of leukemia the next year, researchers from the University of Pennsylvania reported a similar outcome. The FDA authorized the first two CAR-T-cell therapies in less than seven years, and with a third clearance anticipated later this year, research teams worldwide are working quickly to develop additional CAR-T-cell therapies. These cancer treatments have captivated the interest of the general public and researchers, and for good reason.

The appeal of CAR-T-cell therapy is partially due to the amazing manner in which it can completely eradicate cancer in certain patients who have advanced blood malignancies. It's also because the source of the therapy is the patient's own blood, which must be transformed through an extremely intricate manufacturing process into the treatment that is ultimately given back to the patient. This personalized, autologous approach sets CAR-T-cell therapy apart from the majority of other cancer therapies. As Anthony Welch, Ph.D., a project officer in the

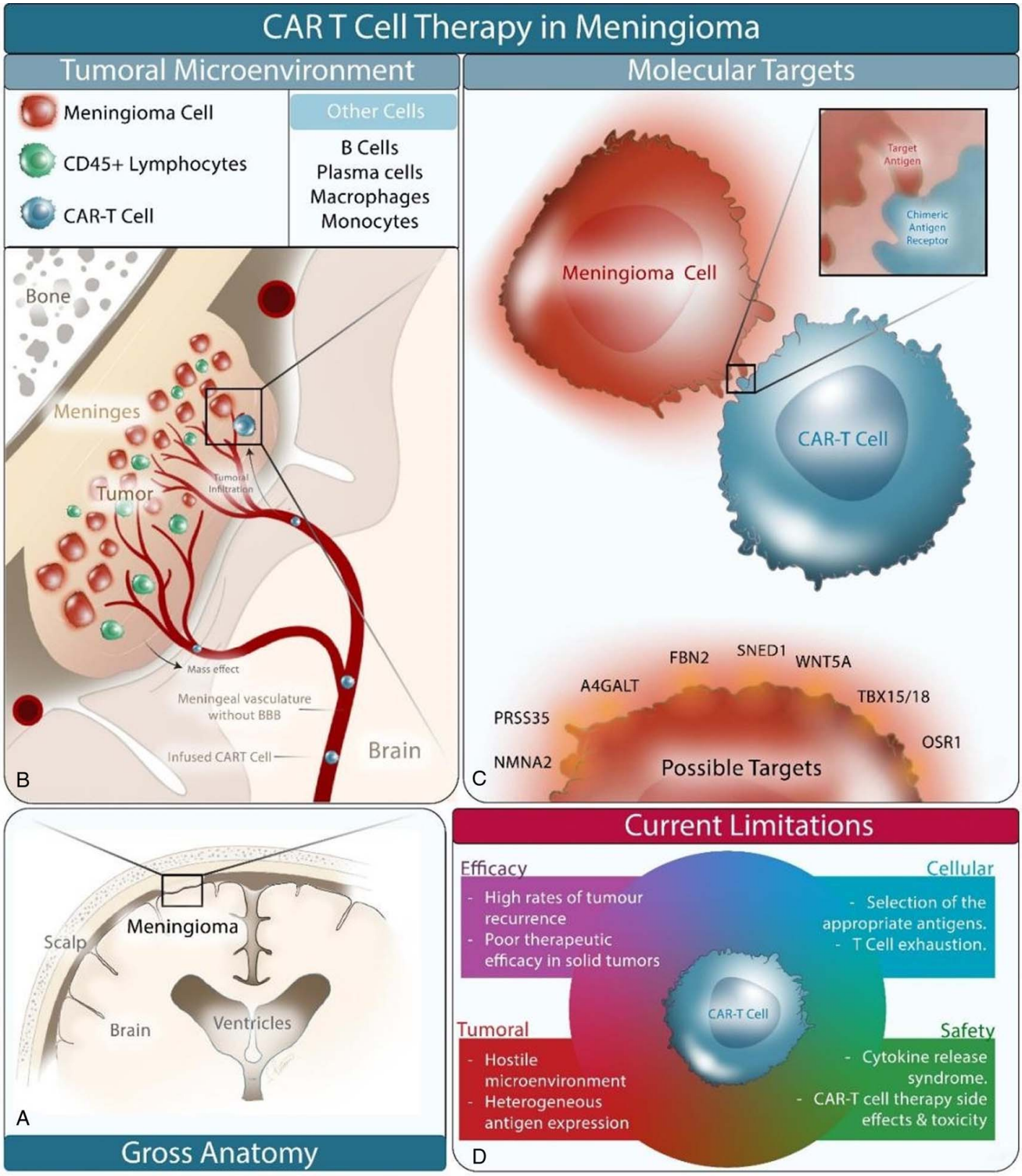


**Figure 1.** This figure reflects the various components and considerations involved in CAR-T-cell therapy for meningioma. The bottom-left section (A) provides an anatomical illustration of a meningioma situated in the meninges, pushing against the cerebral cortex. The illustration shows the tumor's position relative to the scalp, bone, and brain tissue, to illustrate the location. The top-left section (B) shows the meningioma tumoral microenvironment, illustrating the interaction between meningioma cells, CD45 + lymphocytes, and CAR-T cells. Other cell types present include B cells, plasma cells, macrophages, and monocytes. The infiltration of CAR-T cells into the tumor site is illustrated by the blue cells inside the vascular lumen. The right section (C) illustrates the known antigens that could potentially be used as targets for CAR-T-cell therapy. The inset diagram shows a chimeric antigen receptor (CAR) interacting with a target antigen on a meningioma cell. The bottom-right section (D) compares the current limitations of CAR-T-cell therapy in meningioma treatment. The challenges are categorized into efficacy, cellular, tumoral, and safety implications.

Division of Cancer Treatment and Diagnosis (DCTD) at the National Cancer Institute (NCI), aptly stated, "the process is the product with CAR-T cells." However, this process is also costly, intricate, and heavily regulated, presenting significant challenges in the development and deployment of this innovative therapy[28].

One promising approach for treating solid tumors is CAR-T-cell therapy. To target cancer cells specifically while preserving normal tissues and minimizing on-target/off-tumor damage, target antigen (TA) selection is crucial. In clinical trials, the use of CAR-T cells alone to treat different types of solid tumors has shown to be largely ineffective, mostly due to immune escape. While further research is needed to optimize CAR-T-cell treatment for solid tumors, combinatorial techniques with chemotherapy, radiation, and other immunotherapies show promise in overcoming the limits of the immunosuppressive TME[29].

It is evident that CAR-T-cell therapy is highly effective against hematological malignancies, marking a significant advancement in the management of these diseases. Future developments in lowering the toxicity profile of CAR-T-cell therapy, in addition to enhancements in response rate, remission persistence, and preventing CAR-T-cell exhaustion, will serve as a catalyst for increased application in order to significantly improve patient prognosis[29].

The current research into CAR-T-cell therapy for meningiomas is undoubtedly promising, but it is also beset by several significant limitations that must be addressed. A primary challenge lies in the inherent heterogeneity of meningioma tumors, which exhibit variable expression of potential target antigens. This diversity complicates the identification of universal antigens that are consistently expressed across all meningioma subtypes, thereby impeding the development of broadly effective therapies.

Additionally, the immunosuppressive tumor microenvironment of meningiomas, coupled with the restrictive nature of the BBB, presents obstacles to the effective trafficking and infiltration of CAR-T cells into the tumor site. This further complicates the achievement of optimal treatment efficacy.

Moreover, the potential for off-target effects and toxicity poses a considerable risk. Many proposed target antigens for meningiomas are also present on normal tissues, increasing the likelihood of CAR-T cells attacking healthy cells and causing severe adverse events. Therefore, rigorous preclinical testing and target selection are essential to mitigate this risk. Another critical concern is the long-term durability of CAR-T-cell responses in meningiomas. Tumor recurrence remains a significant challenge, necessitating the exploration of strategies to prevent CAR-T-cell exhaustion and maintain their therapeutic persistence.

Despite these challenges, the preclinical evidence supporting the therapeutic potential of CAR-T-cell therapy in meningiomas is compelling. The discovery of novel target antigens and the development of enhanced CAR constructs offer promising avenues for improving both the efficacy and safety of this innovative approach.

The figure provided (Panel D) compares the current limitations of CAR-T-cell therapy in the treatment of meningioma. The challenges are categorized into four main areas: efficacy, cellular, tumoral, and safety implications. These limitations highlight the need for further optimization of CAR-T-cell therapy to overcome the unique barriers posed by solid tumors, such as the immunosuppressive TME, tumor heterogeneity, and off-target effects.

## Future directions

The application of CAR-T therapy to solid tumors is still limited by various factors, including target antigen heterogeneity, poor trafficking, and a hostile tumor microenvironment[30].

The key factor affecting the efficacy of CAR-T therapy is the identification of truly tumor-specific target antigens. Among the antigens investigated, B7-H3 (CD276) was the only antigen found to be highly and homogeneously expressed on tumor cells in a first-in-human study evaluating the bioactivity and safety of B7-H3-targeted CAR-T cells for treating recurrent anaplastic meningioma[31]. However, despite observing a slower local tumor growth, the patient ultimately died after three treatment cycles due to a pulmonary embolism following surgical excision of the rapidly growing distal tumor.

Several factors may have contributed to the limited response observed in this study. To overcome antigen escape relapse, the combination of B7-H3 with another tumor-specific antigen in the CAR design may yield more lasting clinical effects. Additionally, the relatively low infusion dose (maximum dose: $1.5 \times 10^7$ cells) used in this study was lower compared to the doses employed in other successful clinical reports of CAR-T therapy. Furthermore, the route of administration, as intravenous infusion, may have impacted the trafficking and localization of the CAR-T cells to the tumor site, another key obstacle that requires further optimization.

CAR-T-cell therapy represents a new and promising class of cancer treatments, but it is not without its limitations. Researchers are actively exploring ways to engineer CAR-T cells to be safer and more effective using synthetic biology and gene-editing technologies.

While these advanced engineering approaches hold great promise, they also come with increased complexity and potential risks[32]. For example, the viral transduction methods and gene-editing tools used to modify T cells can carry the danger of off-target disruption of genes, which can have unintended consequences. However, as the field of adoptive cell transfer continues to mature, researchers are becoming more comfortable with managing these risks.

An additional challenge is the high cost associated with CAR-T-cell manufacturing, particularly the production of clinical-grade retroviruses. Novel engineering methods, such as the use of non-viral vectors, may help to reduce manufacturing costs and improve the affordability of these transformative therapies[10].

Beyond the challenges with CAR-T-cell therapy for solid tumors like meningioma, recent research has identified a promising T-cell antigen atlas for this disease. A 2023 study has identified several frequently presented meningioma-associated antigens, including NMNA2, PRSS35, A4GALT, FBN2, SNED1, WNT5A, TBX15/18, and OSR1. While the biological roles of most of these newly discovered candidate antigens in meningioma or other tumor types are not yet fully understood, a few, such as NMNA2 and WNT5A, are known to promote cancer cell survival[33].

The HLA class II peptidome includes meningioma-associated antigens that can be used to elicit a synergistic CD4+ T-cell response. This atlas of meningioma T-cell antigens can be leveraged to design a variety of targeted therapies, including vaccines using the identified antigens (mRNA, protein, and peptide), soluble bispecific constructs as T-cell engagers, or for cellular therapies such as peptide-pulsed dendritic cells or *ex vivo*

expanded antigen-specific T cells. These approaches can be tailored for both patient-individualized and off-the-shelf therapeutic options[34].

Notably, the potential of targeting HLA class II-restricted antigens has been recently underscored by clinical data highlighting the crucial role of HLA class II and CD4+ T cells in immune-mediated tumor rejection[30,31,35]. Furthermore, detailed knowledge of the natural HLA class II antigen presentation patterns will allow for the development of multi-epitope peptide vaccines containing both HLA class I- and HLA class II-restricted targets. This strategy may induce and boost synergistic CD8+ and CD4+ anti-tumor immune responses, potentially enhancing the efficacy of these targeted therapies.

Thus, these limitations necessitate a deeper and wider understanding of the behavior of meningioma cells and endogenous T cells. Future research should focus on more extensive T-cell profiling, role of regulator and cytotoxic T cells in mediating tumor growth, and receptor profiling of cancerous meningioma cells. There is a need for clinical trials, particularly including a diverse cohort of patients in order to generate results that show inclusivity. Small steps towards this direction include animal studies evaluating the safety of such administration, as well as in-vitro cell assays to have a better understanding of the mechanisms at play.

The research findings on CAR-T-cell therapy for meningiomas have profound clinical implications, particularly for the management of atypical and anaplastic subtypes, which pose significant treatment challenges. Current modalities often fail to provide durable responses, highlighting the urgent need for new therapeutic strategies. CAR-T-cell therapy represents a novel and potentially transformative approach to treating these tumors, offering a glimmer of hope where traditional treatments fall short.

Should ongoing research successfully address the existing limitations and demonstrate the safety and efficacy of CAR-T-cell therapy for meningiomas, it could reveal a new standard of care for these patients. Positive clinical trial outcomes could lead to regulatory approval of CAR-T-cell therapies specifically tailored for meningioma treatment, providing a much-needed therapeutic alternative for patients with limited options.

Furthermore, the insights gained from studying the tumor-immune microenvironment and identifying target antigens in meningiomas could have broader implications for neuro-oncology. These findings may facilitate the development of other immunotherapeutic approaches, such as checkpoint inhibitors or bispecific antibodies, that could be used in conjunction with CAR-T-cell therapy to enhance overall treatment efficacy. This research holds the potential to revolutionize the management of meningiomas and potentially extend its impact to a wider range of neurological cancers, offering renewed hope for patients dealing with these challenging and devastating diseases.

### *Take-home message*

Using of CAR-T-cell therapy might provide promising treatment strategy for the treatment of meningioma, Tang and colleagues have reported their experience with administering low-dose B7-H3 targeting CAR-T infusions via an Ommoya port. In response to therapy, the patient experienced no significant side effects from the treatment, and elevated levels of various cytokines are detected in CSF. However, on imaging, no definitive signs of tumor regression were found, that's why to make conclusions about the potential of CAR-T therapy for refractory meningiomas, more studies investigating appropriate dosing and alternative targets are required[35].

Although CAT-T therapy has demonstrated anti-tumor efficacy in hematological malignancies treatment, its application to solid tumors is still restricted due to multiple factors like target antigen heterogeneity, trafficking and hostile tumor microenvironment[30].

CAR-T cells can be engineered to target specific antigens expressed on the surface of meningioma cells, such as B7-H3, which has been found to be highly expressed in certain types of meningiomas. This specificity minimizes damage to normal tissues and enhances the therapeutic efficacy against the tumor[36].

### *Overview of weaknesses*

The application of CAR-T-cell therapy for meningioma is constrained by the limited number of clinical trials specifically targeting this disease. This limitation affects the breadth and depth of available data, making it difficult to draw comprehensive conclusions about its efficacy and safety in treating meningioma.

The chimeric antigen receptor T cell in solid tumors have not yet shown the same kind of impressive results as they observed for hematological malignancies, both the microenvironment and tumor cells are involved in numerous variables. The main challenges are the absence of particular target antigens and the severe, sometimes fatal toxicities caused by on-target off-tumor toxicities. Moreover, the chronic inflammation are frequently found in the tumor microenvironment, immunological cells and immunosuppressive can lower CAR-T-cell efficiency and aid antigen escape[37].

CAR-T-cell therapy in meningioma can present several side effects, some of which can be severe. However, toxicity consider to be a major problem because of the potential for immune-related side effects (off-tumor toxicities targeting the lung, brain, and heart[37]. Cytokine release syndrome (CRS) usually appears 1–2 weeks post-dosage, CRS present with a variety of symptoms including high fever, chills, hypotension, tachycardia, headache, dyspnea, respiratory failure, and even potentially fatal multi-organ failure are seen in patients. Multiple inflammatory cytokines, including IL-6, interferon gamma (IFN-γ), IL-1, IL-2, and IL-10, are released and cause CRS[29].

The second most frequent side effect is the possibility of neurotoxicity, the term ICANS (Immune effector Cell-Associated Neurotoxicity Syndrome) is refers to a spectrum of symptoms such as difficulty speaking and understanding, aphasia, confusion, agitation, seizures, abnormalities of cranial nerve and visual hallucinations. Additional major side effects that may occur are plasma electrolyte level abnormalities (potassium, sodium or phosphorus), anemia, leukopenia and neutropenia, which increase the risk of infections, bleeding[37].

## Conclusion

In conclusion, the emerging field of CAR-T-cell therapy and other T-cell applications present promising avenues for the treatment of meningioma. While traditional therapies have shown limited efficacy, innovative approaches harnessing the power of the immune system offer new hope for patients with this challenging disease. The detailed atlas of meningioma T-cell antigens

presented here can inform the design of a variety of targeted immunotherapies, including vaccines, T-cell engagers, and cellular therapies. Our review has comprehensively summarized all key findings in this field, and we found there is still a need for a large scale of development, particularly for the generation of rigorous evidence.

Further research and clinical trials are needed to fully understand the potential for these therapies and optimize their effectiveness in improving outcomes and quality of life for meningioma patients. With continued advancements in immunotherapy and personalized medicine, we are on the brink of transforming the landscape of meningioma treatment, providing renewed optimism for patients and clinicians.

To optimize CAR-T-cell therapy for meningioma, future research should enhance CAR-T-cell persistence, target tumor heterogeneity, and conduct extensive clinical trials for safety and efficacy. Collaboration between clinicians and researchers is crucial for translating these findings into practice. Preliminary animal studies and in-vitro cell line assays can help evaluate the efficacy of CAR-T therapy in meningioma cells. Meningioma, being a tumor that is predominantly influenced by hormones, the interaction between CAR-T therapy and endogenous hormones is still an area that hasn't been explored in literature.

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## Consent

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## Author contribution

All authors have contributed equally.

## Conflicts of interest disclosure

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## References

[1] Kotecha RS, Junckerstorff RC, Lee S, *et al*. Pediatric meningioma: current approaches and future direction. J Neurooncol 2011;104:1–10.
[2] Ostrom QT, Cioffi G, Gittleman H, *et al*. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21(suppl 5):v1–100.
[3] Anzalone CL, Glasgow AE, Van Gompel JJ, *et al*. Racial differences in disease presentation and management of intracranial meningioma. J Neurol Surg B Skull Base 2019;80:555–61.
[4] Zhao L, Zhao W, Hou Y, *et al*. An overview of managements in meningiomas. Front Oncol 2020;10:1523.
[5] Beyar-Katz O, Gill S. Advances in chimeric antigen receptor T cells. Curr Opin Hematol 2020;27:368–77.
[6] Zhang X, Zhu L, Zhang H, *et al*. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. Front Immunol 2022;13:927153.
[7] Chintala NK, Restle D, Quach H, *et al*. CAR T-cell therapy for pleural mesothelioma: rationale, preclinical development, and clinical trials. Lung Cancer 2021;157:48–59.
[8] Yang YH, Liu JW, Lu C, *et al*. CAR-T cell therapy for breast cancer: from basic research to clinical application. Int J Biol Sci 2022;18:2609–26.
[9] Schepisi G, Cursano MC, Casadei C, *et al*. CAR-T cell therapy: a potential new strategy against prostate cancer. J Immunother Cancer 2019;7:258.
[10] Zhang XW, Wu YS, Xu TM, *et al*. CAR-T cells in the treatment of ovarian cancer: a promising cell therapy. Biomolecules 2023;13:465.
[11] Guzman G, Reed MR, Bielamowicz K, *et al*. CAR-T therapies in solid tumors: opportunities and challenges. Curr Oncol Rep 2023;25:479–89.
[12] Luksik AS, Yazigi E, Shah P, *et al*. CAR T cell therapy in glioblastoma: overcoming challenges related to antigen expression. Cancers 2023;15:1414.
[13] Salmon H, Franciszkiewicz K, Damotte D, *et al*. Matrix architecture defines the preferential localization and migration of T cells into the stroma of human lung tumors. J Clin Invest 2012;122:899–910.
[14] Levine BL, Miskin J, Wonnacott K, *et al*. Global manufacturing of CAR T cell therapy. Mol Ther Methods Clin Dev 2016;4:92–101.
[15] Kenderian SS, Ruella M, Shestova O, *et al*. CD33-specific chimeric antigen receptor T cells exhibit potent preclinical activity against human acute myeloid leukemia. Leukemia 2015;29:1637–47.
[16] Zhang Z, Liu S, Zhang B, *et al*. T cell dysfunction and exhaustion in cancer. Front Cell Dev Biol 2020;8:17.
[17] Medici G, Freudenmann LK, Velz J, *et al*. A T-cell antigen atlas for meningioma: novel options for immunotherapy. Acta Neuropathol 2023;146:173–90.
[18] Sahab-Negah S, Gorji A. Meningioma tumor microenvironment. Adv Exp Med Biol 2020;1296:33–48.
[19] Bhowmik A, Khan R, Ghosh MK. Blood brain barrier: a challenge for effectual therapy of brain tumors. Biomed Res Int 2015;2015:320941.
[20] Abbott NJ, Patabendige AA, Dolman DE, *et al*. Structure and function of the blood-brain barrier. Neurobiol Dis 2010;37:13–25.
[21] Garzon-Muvdi T, Bailey DD, Pernik MN, *et al*. Basis for immunotherapy for treatment of meningiomas. Front Neurol 2020;11:945.
[22] Turner CP, McLay J, Hermans IF, *et al*. Tumour infiltrating lymphocyte density differs by meningioma type and is associated with prognosis in atypical meningioma. Pathology 2022;54:417–24.
[23] Wang JZ, Nassiri F, Bi L, *et al*. Immune profiling of meningiomas. Adv Exp Med Biol 2023;1416:189–98.
[24] Fang L, Lowther DE, Meizlish ML, *et al*. The immune cell infiltrate populating meningiomas is composed of mature, antigen-experienced T and B cells. Neuro Oncol 2013;15:1479–90.
[25] Borch JS, Haslund-Vinding J, Vilhardt F, *et al*. Meningioma-brain crosstalk: a scoping review. Cancers 2021;13:4267.
[26] Li W, Wu L, Huang C, *et al*. Challenges and strategies of clinical application of CAR-T therapy in the treatment of tumors-a narrative review. Ann Transl Med 2020;8:1093.
[27] Engineering CAR T-Cell therapy to overcome limitations. (2023, February 8). Cancer.gov. https://www.cancer.gov/news-events/cancer-currents-blog/2023/car-t-cell-therapies-overcoming-limitation

[28] NCI aims to boost CAR T-Cell therapy clinical trials. Cancer.gov. Accessed 23 April 2020. https://www.cancer.gov/news-events/cancer-currents-blog/2020/car-t-cell-nci-manufacturing-clinical-trials
[29] Lin YJ, Mashouf LA, Lim M. CAR T cell therapy in primary brain tumors: current investigations and the future. Front Immunol 2022;13:817296.
[30] Newick K, O'Brien S, Moon E, *et al*. CAR T cell therapy for solid tumors. Annu Rev Med 2017;68:139–52.
[31] Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nat Rev Clin Oncol 2019;17:147–67.
[32] Monjezi R, Miskey C, Gogishvili T, *et al*. Enhanced CAR T-cell engineering using non-viral Sleeping Beauty transposition from minicircle vectors. Leukemia 2017;31:186–94.
[33] Kreiter S, Vormehr M, van de Roemer N, *et al*. Mutant MHC class II epitopes drive therapeutic immune responses to cancer. Nature 2015;520:692–6.
[34] Schumacher T, Bunse L, Pusch S, *et al*. A vaccine targeting mutant IDH1 induces antitumourimmunity. Nature 2014;512:324–7.
[35] Tang X, Liu F, Liu Z, *et al*. Bioactivity and safety of B7-H3-targeted chimeric antigen receptor T cells against anaplastic meningioma. Clin Transl Immunol 2020;9:e1137.
[36] Haydar D, Houke H, Chiang J, *et al*. Cell-surface antigen profiling of pediatric brain tumors: B7-H3 is consistently expressed and can be targeted via local or systemic CAR T-cell delivery. Neuro Oncol 2021;23:999–1011.
[37] Gatto L, Ricciotti I, Tosoni A, *et al*. CAR-T cells neurotoxicity from consolidated practice in hematological malignancies to fledgling experience in CNS tumors: fill the gap. Front Oncol 2023;13:1206983.