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Review

Nanoengineered immune check point inhibitors delivery for targeted brain cancer treatment: Current status and future perspectives

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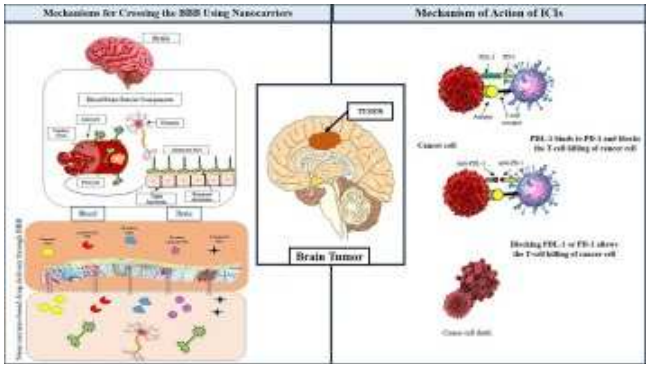
Abstract

Brain tumors create special difficulties because of their position and the protective covering of blood brain barrier (BBB) that restricts efficient medication access. Treatment alternatives such as surgery and chemotherapy demonstrate poor performance against severe brain tumors. The use of immune checkpoint inhibitors (ICIs) hints at effective cancer therapy; however, their application to brain cancer faces challenges due to inefficient delivery through the BBB and the tumor's suppressive environment. Nanoengineering can increase the transport of ICIs to brain tumors. Numerous nano-delivery systems such as liposomes and micelles have explored ways to avoid the BBB via transcytosis and the EPR mechanism. Functionalization of nanocarriers

enhances targeting tumor cells and improves treatment accuracy. New developments involve delivering ICIs together with adjuvants to change the TME and focusing on immune cells such as TAMs and Tregs to boost immunity against tumors. Nanoengineered ICIs have shown effective improvement in animal models by reducing toxicity and enhancing efficacy. Converting these successes into real clinical trials is not easy as they face regulatory concerns and safety challenges. Clinical trials currently examine the use of nanocarriers for treating brain cancer; however, scalability' and 'long-term safety' continue to pose challenges. Future approaches will focus on combining customized medicine with advanced nanotechnology and AI to refine treatment methods. Despite obstacles ahead, nanotechnology-based ICIs offer a hopeful approach to enhance brain cancer efficacy and address existing therapeutic constraints.

Graphical abstract



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Introduction

Brain cancer, particularly glioblastoma multiforme (GBM), presents significant challenges in treatment due to its invasive nature and the complexities of the tumor microenvironment [1]. Traditional therapies such as surgery and radiation are typically ineffective, leading to a median survival of only 12 to 15 months after diagnosis [2]. Recently immune checkpoint inhibitors (ICIs) have transformed the landscape of cancer therapy by increasing the capacity of the immune system to recognize and eradicate cancer cells [3]. Nevertheless, their use for the treatment of brain tumor remains limited by the blood brain barrier (BBB) and immunosuppressive nature of the tumor microenvironment (TME) [4]. Advanced nanotechnology has recently been proven to enhance drug delivery systems and can increase cellular targeting specificity of ICIs to tumor sites while reducing systemic toxicity [5]. Enhancing drug accumulation at tumors and remodeling the TME to support anti-tumor immune responses via nanoengineered platforms can improve therapeutic outcomes for GBM patients.

Immune Checkpoint Therapy in combination with Nanotechnology presents a potentially promising way forward for addressing current barriers in brain cancer treatment. Drug release

from such nanoengineered systems can be designed to respond to specific TME conditions including acidic pH or hypoxia to improve therapeutic efficacy [6]. For instance, by using advanced delivery methods, researchers are currently developing new strategies to use ICI combined with nanomedicine to achieve not only stronger T cell responses but confronting the tumor heterogeneity and resistance mechanism problems [7], [8]. This review emphasizes on current developments of nanoengineered ICI delivery for targeted brain cancer treatment, with future perspectives for their clinical applications highlighted and the need for further research underlined.

A heterogeneous group of neoplasms, brain cancers emerge from diverse cell types found in the central nervous system (CNS). There are various kinds, from benign, slow-growing tumors to highly malignant and aggressive forms, like gliomas. Glioblastomas, categorized as grade IV gliomas, are the leading malignant brain tumors and are known for their fast cell development, broad invasiveness, and irresponsibility to standard treatment options [9], [10], [11]. Since severe approaches to therapy might seriously impair brain functioning, the location of these tumours poses significant complications. Irrespective of years of investigation, the outlook for patients with brain cancer is still not favorable, stressing the demand for new treatment methods that can break through the limitations of current therapies [12].

In 2019, the Global Cancer Observatory reported that there was a significant yearly incidence of brain and CNS malignancies, with 347,992 new cases reported annually [13]. Gliomas, particularly GBM, make up nearly 80% of the malignant brain tumors observed in adults. The frequency of gliomas rises with age, and the average age at diagnosis for GBM is 64 years [14]. The median survival rate for individuals with GBM is around 15 months, and less than 10% of patients survive for five years despite invasive treatment regimens that include surgery, radiation, and chemotherapy [15].

Brain cancer mortality rates are closely related to the disease's rapid progression and lack of available effective therapies. In comparison to other cancers, brain tumors are especially deceptive due to their placement in the CNS, where tiny tumors may cause serious neurological symptoms [16], [17]. In many counties, brain cancer has become the foremost cause of cancer-related deaths among children, bringing attention to the necessity for progress in treatment alternatives. In addition, the severe invasiveness of malignant brain tumors, especially GBM, usually prohibits full surgical resection, leading to significant recurrence rates and limited survival betterment despite multimodal treatments [18].

The treatment of brain cancer, particularly high-grade gliomas, entails a multifaceted method that combines surgery, radiotherapy, and chemotherapy. The first treatment approach is usually surgery, which seeks to accomplish maximal safe resection as its goal [19]. Nevertheless, because of gliomas' infiltrative characteristics, a complete resection through surgery is seldom possible without incurring considerable neurological damage. Surgery alone is often inadequate for eliminating cancer completely because tumor cells often infiltrate nearby healthy brain tissue. Which contributes to the dismal long-term results for many brain cancer patients, post-surgical recurrence is almost inevitable [20].

Following surgery, radiotherapy is usually used to address the remaining tumor cells. Fractionated external beam radiation, delivered over several weeks, represents the standard protocol. Though radiotherapy can suppress tumor development, it is often linked to serious side effects, including radiation necrosis and cognitive issues, because of the damage caused to healthy brain tissues nearby [21]. Innovations such as intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery (SRS) have advanced targeting precision, but the sensitivity of healthy brain tissue to radiation continues to impose limitations [22].

An integral part of brain cancer treatment played by chemotherapy includes temozolomide (TMZ) as the chemotherapeutic agent most often used for gliomas [23], [24]. Used in combination with radiotherapy, TMZ is an alkylating agent that successfully crosses the BBB and has improved survival for patients with GBM [25]. Nonetheless, TMZ advantages are restricted by several elements, notably the rise of resistance in tumor cells and the drug's failure to cross the BBB with enough concentration to effectively kill tumor cells. Also, patients without methylation at the O6-methylguanine-DNA methyltransferase (MGMT) promoter exhibit greatly diminished responsiveness to TMZ, which limits its usefulness [26]. Even though this multimodal strategy has improved immediate results, it fails to fulfill the needs for sustainable control of brain cancers, especially GBM. The nearly inevitable occurrence of tumor recurrence after initial treatment illustrates the critical requirement for new treatment approaches, including immunotherapy and nanoengineered drug delivery systems, capable of targeting remaining tumor cells and improving outcomes.

One of the most important challenges in treating brain cancer is the BBB. A highly discerning endothelial barrier, the BBB shields the brain by blocking the entrance of dangerous compounds from the circulatory system [27]. This barrier is essential for maintaining brain homeostasis, but it also significantly impairs the capacity of therapeutic substances, such as biologics and chemotherapeutic drugs, to reach brain tumours [28]. Many potentially useful medications are unable to pass the BBB due to tight junctions between endothelial cells and the activity of efflux transporters, particularly P-glycoprotein (P-gp). The barrier allows only small, lipophilic molecules and those with particular transport mechanisms to pass through efficiently [29].

The challenge posed by the BBB is substantial for ICIs, which have transformed cancer therapy by blocking inhibitory pathways that stop immune cells from attacking tumors [30]. Large monoclonal antibodies such as anti-PD-1 and anti-CTLA-4 are part of ICIs, which have problems crossing the BBB in adequate quantities for a therapeutic response in brain tumors [31]. Also, the immune-privileged position of the brain provides more complexity. The CNS has developed strategies to limit the immune response, thus reducing inflammation but also lessening the impact of ICIs, which rely on the activation of immune cells to target tumors [32].

Several different strategies have been investigated to overcome the BBB for drug delivery related to brain cancer treatment. These strategies comprise the chemical alteration of treatment agents to improve their lipophilicity, the use of transport systems that are carrier-mediated, and the development of nanoparticles able to bypass or momentarily open the BBB for drug delivery purposes [33]. There is potential shown by nanoparticles, notably in preclinical investigations for the increased delivery of ICIs to brain tumors. These nanoengineered technologies can be

modified to target distinctive receptors found on brain tumor cell surfaces, enhancing drug buildup at the tumor locality while reducing systemic toxicity [34]. As an additional feature, nanoparticles can respond to specific stimuli within the tumor microenvironment and thereby deliver ICIs in a more controlled and localized manner.

Section snippets

Immune checkpoint inhibitors (ICIs)

ICIs are the most transformative category of therapies, which use the body's own immune system to combat cancer. Cancer cells can escape the immune system by using immune checkpoint proteins, which are protective mechanisms of the immune system. ICIs works by preventing such inhibitory signals from occurring because they unchain or enable the immune cells, or the T Lymphocytes to identify and kill the tumor cells (Fig. 1). Though through preclinical and clinical, ICIs have demonstrated potency …

Nanoengineering for drug delivery

Nanotechnology has introduced unique changes into various fields and has displayed great potential when used in medication, particularly the delivery of drugs. Nanoengineering potential to produce nanometer-sized multifunctional materials provides the possibility to avoid such drawbacks of the conventional therapies as low solubility of many drugs, their low availability for action, and non-selective action. These tailored nanocarriers have demonstrated the ability to improve the delivery and …

Nanoengineered delivery of immune checkpoint inhibitors

ICIs have transformed the treatment of cancer by employing the immune system of the body for attacks on cancer cells. However, the application of ICIs to treat brain cancers like Glioblastoma suffer from considerable challenges which include the inability of large molecules to cross the BBB and the fact that GBM has suppressive TME [68]. Nanotechnology seems to overcome all these challenges and thus presents a more effective means of delivering ICIs to brain tumors. Consequently, nanoengineered …

Mechanisms for crossing the BBB using nanocarriers

Due to their large molecular size, it is difficult to transport ICIs across the BBB which is not an easy process of delivering therapeutic agents to the brain. Nanoparticles can use the following mechanisms to overcome this barrier: receptor mediated transcytosis and passive diffusion through the EPR effect [33]. Such approaches allow nanoparticles to easily penetrate the BBB and deliver a therapeutic load to brain tumors, enhancing the effectiveness of therapy and limiting systemic toxicity. …

Nanocarrier types for ICIs

Based on the stability, targeting, and release patterns, several nanocarrier forms have been studied to deliver immune checkpoint inhibitors for brain cancer therapy. These nanocarriers can be altered to fulfill drug delivery requirements, such as ICI bioavailability at the TME and BBB penetration. Modern material science was utilized by these nanocarriers to simultaneously improve ICI-associated off-target effects and toxicity downregulation, improving therapeutic outcomes. The four types of …

Advances in targeting strategies

There has been a better understanding of the method of delivering ICIs to brain tumor cells in the last few years. These strategies target to enhance the ability of selectively delivering therapeutic agents into the tumor region while reducing the side effects of ICIs. The methods used in these strategies of delivery ensure that the ICIs get to the precise tumor-associated characteristics like TME, surface receptors, and overexpressed antigens. Some of the significant developments in this area …

Current clinical trials and preclinical studies

The field of nanoengineered ICI delivery systems has gained significant momentum in both preclinical and clinical settings. Preclinical studies using animal models have shown promising results in enhancing the efficacy of ICIs, while clinical trials are beginning to evaluate the safety and effectiveness of these approaches in human patients with brain cancer. …

Future perspectives and challenges

Studies on nano-engineered solutions for ICIs are developing rapidly. This signals extensive prospects for new developments and applications in brain cancer treatment. Key issues must be resolved to guarantee a smooth flow of these technologies from the testing phase to patient care. This section examines the development of novel nanotechnologies and their relevance in precision medicine while addressing hurdles of AI regulation and manufacturing safety.

Advancements in nanotechnology are …

Conclusion

Nano-engineered ICIs create an innovative method to solve the distinct obstacles in brain cancer interventions. The application of polymeric and lipid nanoparticles enables ICIs to bypass the blood–brain barrier more effectively. This positively affects treatment results and lowers risks associated with systemic interactions. Utilizing these systems directs therapy toward brain tumors to stimulate immune responses in the tumor environment. Results from animal models reveal that nanotechnology …

Consent for publication

“Not applicable” as this manuscript does not contain data from any individual person. …

Ethical approval and consent to participate

Not Applicable. This is a review paper and do not involve direct research on humans or animals. …

CRediT authorship contribution statement

Juan Liu: Formal analysis, Data curation. **Yichao Wang:** Data curation, Writing – review & editing. **Zhidu Song:** Writing – original draft, Investigation, Formal analysis. **Yukai Zhang:** Writing – review & editing, Supervision, Data curation, Conceptualization. …

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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