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Review Article

Opportunities and Challenges in Overcoming the Blood-Brain Barrier to Treat Brain Cancer Along with Resection

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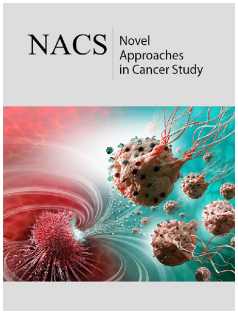

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Abstract

The prognosis for primary and secondary brain malignancies is still poor despite substantial advancements in research. The Blood-Brain Barrier (BBB) is a complicated and distinct semi-permeable membrane that safeguards the brain's equilibrium. It does, however, provide a serious obstacle to the administration of medications to the tumor and brain. It is known that certain brain tumors can damage the integrity of the Blood-Brain Barrier (BBB), resulting in a very diverse vasculature known as the Blood-Tumor-Barrier (BTB). Research in this field has focused on finding ways to get beyond these barriers to increase anticancer therapies' penetrability. The brain microenvironment has the potential to hinder the efficacy of medications intended to treat primary brain tumors and their metastases. Research in this field has focused on finding ways to get beyond these barriers to increase the penetrability of anticancer therapies. More knowledge of the BBB and BTB and the existing approaches to overcoming these obstacles will make it possible to create novel and more potent brain tumor treatment plans. The methods currently undergoing preclinical or clinical investigation, including molecular, biological, and physical processes to overcome the BBB or BTB, are detailed in this review along with the strategies that have been studied to avoid or modify the cellular and molecular barriers of both the BBB and the BTB.

Introduction

The Blood-Brain Barrier

A complex and one-of-a-kind semi-permeable membrane, the Blood-Brain Barrier (BBB) acts as a barrier to preserve homeostasis in the brain. The Blood-Brain Barrier (BBB) covers 20m2 and is about 600km long in the human brain [1,2]. It is made up of about 100 billion capillaries. With a diameter of around 7.5μm, each capillary permits blood flow to occur within 10μm of every brain cell. By blocking molecules bigger than 400 Daltons from entering the brain via the circulation, this physical barrier selectively shields the brain's microenvironment from potentially hazardous external chemicals [3,4]. The BBB controls how much oxygen enters the brain and how much carbon dioxide and metabolites are expelled. Thirty percent of the endothelium layer is surrounded by vascular pericytes, which regulate the expression of genes unique to endothelial cells' BBB and the diameter of the arteries [5-7]. The exterior wall of the endothelium is home to perivascular astrocytic end-feet, which upregulates BBB characteristics and fortifies tight junctions. Adjacent vascular endothelial cells' tight connections limit paracellular migration and promote transcellular migration. While larger hydrophilic molecules, such peptides or proteins, require transport systems, smaller lipophilic molecules diffuse passively into the brain [8]. The absence of fenestrae and efflux transporters, along with the continuity of tight junctions, create separate luminal and abluminal compartments in the Blood-Brain Barrier (BBB), allowing for stringent regulation and control between the two [9]. The structure of capillary beds in the neuroparenchyma, which is made up of ECs connected by Tight Junctions (TJs), encircled by a specialized basal lamina shared with pericytes and astrocytic end feet, and sparsely connected by neuronal endings and microglia, was characterized in part by preclinical and clinical observations in

the decades that followed [10]. Collectively, these cells determine the BBB's physical characteristics and the construction of the CNS endothelium. Particularly controlled transport mechanisms within these cellular and extracellular networks enable the controlled inflow of circulating molecules necessary for Central Nervous System (CNS) function while facilitating the effective outflow of harmful cellular waste back into the circulation [11]. While certain immune cell populations can "loosen" and penetrate the Blood-Brain Barrier (BBB) during neuroinflammation, others can heal injured neurological tissue, despite the CNS being thought of as having a distinct immune system [12]. The Neurovascular Unit (NVU), which is made up of neuro-parenchymal cells and the BBB endothelium, functions as a "gatekeeper" in the central nervous system, strictly regulating the passage of substances and cells between cells and between cells [13].

Heterogeneity of the BBB in Brain Tumors

Because the brain is a small place, the development of tumors can compress veins and reduce blood flow even in peritumoral areas [14]. Additionally, when brain tumor lesions grow, the NVU acquires distinct characteristics in the tumor core as opposed to the tumor's perimeter and the neuroparenchyma, the latter of which has an intact blood-brain barrier. The vasculature around the main brain tumor gets more varied as the tumor progresses and brain metastases form [15]. Vascular and neuronal viability may be directly jeopardized by alterations brought about by an increasing malignant tumor, both locally and distantly. Because tumor growth causes a significant alteration in the vasculature, the multiplying cancer cells' need for nutrients necessitates coopting preexisting arteries or generating new ones by angiogenesis. Tumors can also enhance blood vessel supply through other ways, such as: postnatal vasculogenesis, intussusception, vascular mimicry and trans differentiation [16-18]. Brain tumors and other forms of tumors can have different architectures and convoluted vascular systems. Hypoxia and an acidic microenvironment caused by vascular dysfunction during tumor progression, partly due to dysregulated expression of angiogenic factors like Vascular Endothelial Growth Factor (VEGF), fuel tumor progression through hypoxia-inducible factor 1α (HIF1α)-induced transcriptional programs. In mice with brain tumors, blocking VEGF signaling temporarily removes the immature and leaky arteries while actively reshaping the remaining vasculature to more nearly resemble normal vasculature [19,20]. We have demonstrated the effect of vascular normalization for survival in patients receiving antiangiogenic medications for both newly diagnosed and recurrent glioblastoma. However, the hypoxia that results from anti-angiogenic treatment can make cancer cells more invasive, at least when used in large doses. Moreover, anti-angiogenics at high dosages may reduce BTB permeability, which may have an impact on the delivery of other therapies [21,22]. This is because VEGF itself has the capacity to modulate BBB permeability. Finding the ideal balance between these vascular phenotypes is still a problem for anti-angiogenic treatments for brain metastases and primary brain tumors [23]. The Blood-Brain Barrier (BBB) is disrupted when drugs accumulate more in brain tumors than in the unaffected brain. This is also the case when brain tumour indicators, such as circulating cancer cells from gliomas, are found in the bloodstream. Most people agree that the BTB is "leakier" than the BBB [24]. Disruption of the BTB has been established by imaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), especially with high-grade brain tumors like glioblastoma [25]. In spite of these findings, it is evident that progressing glioblastomas exhibiting a variety of efflux transporters that block the entry of anticancer drugs can have an intact blood-brain barrier [26,27]. Atypical pericyte distribution, loss of astrocytic end feet, and disruption of neural connections are characteristics of BTB. Moreover, the integrity of the blood-brain barrier can be damaged by glioma cells physically displacing astrocytic end feet [28,29]. Brain tumors contain peripheral monocytes and T cell subpopulations, which suggests that the NVU is permeable to circulating immune cells. Additionally, the intratumoural vasculature in brain metastases never fully re-establishes a normal blood-brain barrier, and junctional proteins decline in BTB ECs [30,31]. The BTB preserves important components of the BBB, such as the production of active efflux transporters in ECs and tumor cells, while being classified as a damaged NVU [32].

Drug delivery across the BBB/BTB

The Blood-Brain Barrier (BBB) poses a significant obstacle for therapeutic intervention, although being necessary for proper CNS function. But new knowledge about the structure and function of the BBB and BTB has led to innovative ways to get beyond this obstacle and treat brain tumors, including those that have invaded the peritumoral areas [33,34]. Poor medication distribution within brain tumors can be attributed to any of the aforementioned factors, either directly or indirectly. The NVU creates several obstacles for medications in circulation, including decreased transcytosis, decreased paracellular transport of hydrophilic molecules, and controlled polarized efflux transporters that block neuroparenchyma access to lipophilic synthetic compounds [35-37]. Small hydrophilic substances can enter the brain via the paracellular pathway, while hydrophobic molecules of molecular weight <500 Da (less than 1nm) diffuse transcellularly into the neuroparenchyma when the blood-brain barrier is intact. All the same, a lot of pharmaceuticals that are on the market have a preference for the ABC transporters that are resistant to drugs [38,39]. Therefore, ABC transporters frequently play a role in both improving the BTB's barrier qualities and lowering the pace at which possible medications traverse the Blood-Brain Barrier. The most prevalent ABC transporters are P-gp, which contributes to the poor brain penetration of big (>500 Da) hydrophobic medicines; BCRP, which confers resistance to xenobiotics and non-chemotherapeutic medications; and a number of MDR ABC transporter family members [40].

Drug Modulation to cross the BBB

Peptide-drug combinations and transcytosis modulation

The covalent attachment of a peptide to a drug through certain linkers renders peptide-drug conjugates as prodrugs. They usually consist of a linker between them, a tumor-homing peptide, and a cytotoxic agent. Drugs have been coupled with peptides that are

BBB permeable to create peptide-drug conjugates [41]. Peptide-drug conjugates have changed in the past several years. Peptides can now be produced and purified on a massive scale, and a variety of tumor-targeting peptides have been identified for various cancer types [42]. By choosing a tumor-homing peptide and the appropriate physiochemical characteristics, including solubility and stability, required for conjugation with the therapeutic load, a partially customized treatment may be created. A stable peptide-drug combination with a high binding affinity for the receptor and a peptide unique to the receptor are two essential components of a successful peptide-drug conjugation [43,44]. To deliver the medication into the tumor, the peptide has to bind specifically to a certain receptor on the target tissue's cell surface that is either overexpressed or distinct in cancer cells. To guarantee that the medication will reach the tumor site and release, the peptide-drug conjugate site and linker must not alter the binding affinity to the target receptor or the stability, therefore reducing off-target toxicity [45,46]. Arginine-glycine-aspartic acid, gonadotropin-releasing hormone, somatostatin, epidermal growth factor, and Angiopep-2 are a few of the most often utilized linear and cyclic peptides. With the exception of Angiopep-2, which enters the cells by transcytosis through the Low-density lipoprotein receptor-related protein 10 (LRP-1) transporter, all of these peptides are supplied to cells by endocytosis or adsorptive-mediated transcytosis [47]. Cytotoxic drugs including gemcitabine, Doxorubicin (Dox), daunorubicin, paclitaxel, and camptothecin have frequently been combined with these peptides [48].

Aspartic Acid, Glycine and Arginine (RGD)

Targeting integrins, the tripeptide arginine-glycine-aspartic acid (RGD) motif is a commonly used peptide carrier that facilitates cell adhesion. Many proteins, including fibrinogen, fibronectin, prothrombin, tenascin, and other glycoproteins, have the RGD motif. Integrins, which are overexpressed in brain endothelial cells, freshly created vasculature, and tumor cells, and which are crucial for cell proliferation, invasion, and angiogenesis, are responsible for recognizing RGD. Several high-grade glioma models have been treated with targeted drug delivery using RGD peptide drug conjugates. RGD peptides have been investigated in Phase I/II and Phase III clinical studies for gliomas that are newly diagnosed, progressing, or recurring, and have shown minor anti-tumor benefits [49,50].

Somatostatin (SST)

The neuropeptide somatostatin (SST) is generated by immunological, inflammatory, and neuroendocrine cells. Among its many physiological roles, SST can act as a neurotransmitter, a paracrine regulator, or an endocrine hormone. Humans express SST in many different parts of the body, including the brain, liver, lungs, pancreas, thyroid, gastrointestinal system, and adrenal gland. Somatostatin receptor subtypes 1–5 and SSTR1–5 are the five different GPCR subtypes that mediate the two active forms of SST, SST–14 and SST–28. Both the unidirectional efflux transporter Multidrug resistance protein 2 (Mrp2) on the apical membrane of brain capillary endothelial cells of the BBB and the ATP-powered efflux pump P-glycoprotein (Pgp) on the plasmatic membranes of the endothelial cells of the BBB are thought to be responsible for transporting SST across the BBB [51,52]. Multiple SST receptors are expressed by GBMs, with SSTR1 and SSTR2 being the most often expressed. In GBM models, SST analogues coupled to Dox (or Dox derivatives) or unique peptides have proven to be effective therapeutic targets. Though none of them have advanced to clinical trials, these findings show the effectiveness of altering medications to target the SSTRs in gliomas for effective and precise pharmacological targeting of therapies [53].

Angiopep-2

The low-density Lipoprotein Receptor-related Protein 1 (LRP1) receptor, which is engaged in the intracellular compartment within endosomal vesicles where amyloid precursor protein is taken up and processed, is the source of angiopep-2. Recently, angiopep-2 has gained interest as a promising therapeutic carrier for brain cancers because of its capacity to pass the blood-brain barrier through receptor-mediated transcytosis after binding to LRP1. Angiopep-2 has been used to transfer proteins and genetic elements as well as cancer treatments as Dox, paclitaxel, camptothecin, and etoposide [54-57]. Furthermore, it has been demonstrated that Guo et al. [57] statin-loaded Angiopep-2-anchored nanoparticles (S@A-NPs) enhance LRP1 expression in brain endothelial. The nanoparticles were also seen to improve median survival in a brain metastatic mouse model when loaded with Dox also seen to improve median survival in a brain metastatic mouse model when loaded with Dox cells and brain metastatic tumor cells *in vitro*, hence improving transcytosis. Additionally, the nanoparticles were seen to increase a brain's median survival. Different formulations of nanoparticles, like the one created by Khan et al. [58] and associates, are designed to avoid being cleared by LRP1. In mice models of breast cancer brain metastases, they found that NPs-K-s-A, or nanoparticles coupled to an MMP1-sensitive fusion peptide combining HER2-targeting K and LRP1-targeting angiopep-2 (A), exhibited a greater brain accumulation than angiopep-2-decorated NPs. In clinical studies, ANG1005, which consists of paclitaxel conjugated to Angiopep-2, has been investigated for the treatment of high-grade gliomas exhibiting early clinical activity and brain metastases [56-58].

Drug-Carrying Nanoparticles that Can Traverse the BBB

Recent developments and the progress of nanotechnology present a viable avenue for medicine administration for individuals with central nervous system disorders. The engineering technique of nanotechnology has potential medicinal uses, such as the creation of nanoparticles as medication carriers to improve delivery across the blood-brain barrier. Delivering nanoparticles has several advantages, such as its capacity to penetrate the blood-brain barrier, enhanced permeability and retention in cancer cells, and little impact on nearby healthy tissues while remaining non-invasive for patients. Stable elements (inorganic) like iron and gold, or organic nanoparticles like liposomes, micelles, and polymer nanoparticles, are the basis for drug carrier nanoparticles [59-61]. Figure 1 depicts the different types of nanoparticles.

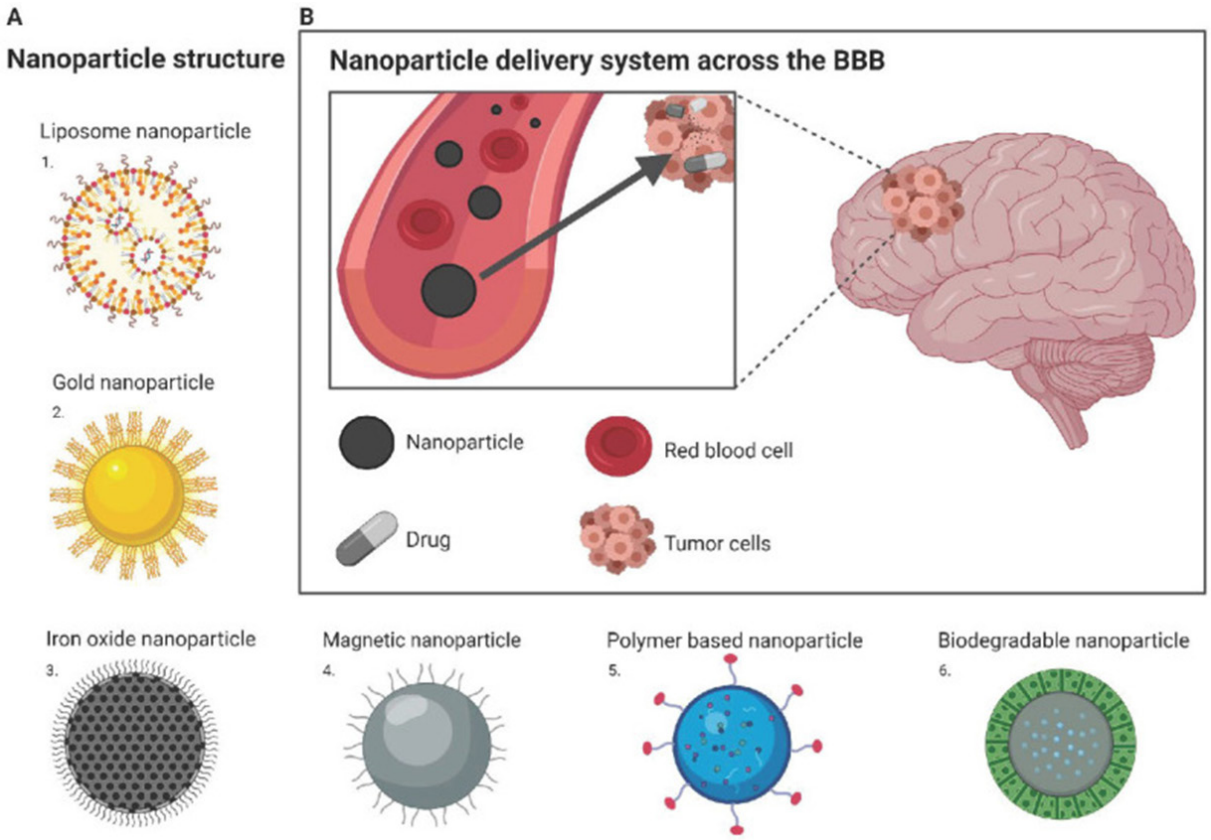

Figure 1: Nanoparticle medication delivery to the brain (A). Structure of several nanoparticles: 1. Liposome nanoparticle; 2. Gold nanoparticle; 3. Iron oxide nanoparticle; 4. Magnetic nanoparticle; 5. Polymer-based nanoparticle; and 6. Biodegradable nanoparticle (B). Nanoparticle distribution technique via the BBB: The drug is contained within a nanoparticle, which may flow freely from the bloodstream to the tumor location in the brain.

Mechanical Disruption of the Blood-Brain Barrier/ Blood-Tumor Barrier

Focused ultrasound

By concentrating sound waves into a small area, Focused Uddltrasound (FUS) can produce targeted disruption of the blood-brain barrier and increased permeability. FUS can concentrate acoustic energy to a focal location, hence providing reversible disruption of the BBB to improve permeability. Combining FUS with commercially accessible medications is a generally safe method that may be tailored to the patient's chemo plan. The addition of microbubbles to the FUS technique has reduced the amount of damage to the surrounding healthy brain tissues by concentrating the action of FUS on the blood vessel walls. Circulating microbubbles and the low-intensity FUS interact closely in MB-facilitated FUS, leading to a transient disintegration of tight junctions and an increase in BBB permeability. Studies have demonstrated that most of the time, repeated use of FUS and microbubbles to open the BBB over a lengthy period of time (4–20 months) did not cause oedema [62-64]. However, on the day after FUS and microbubble application, there was a notable increase in response time during a neurotoxicity test task; This increased reaction time recovered to baseline within 4-5 days, indicating the method's safety. Several medications, including as Dox, TMZ, BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), bevacizumab, and MTX, have been effectively coupled with microbubbles and FUS in preclinical models. It has progressed even further to be utilized with macro-agents such stem cells, tiny interfering siRNA, and magnetic nanoparticles. Furthermore, focused ultrasound is presently being tested in clinical studies for dementia caused by Alzheimer's disease, Parkinson's disease, and breast cancer that has spread to the brain, as well as brain cancers such as GBM and low-grade gliomas. These results offer early proof that FUS can temporarily raise BBB permeability and raise local anticancer medication concentrations to further impede the growth of tumors. The fact that FUS is typically limited to tiny brain volumes or locations, and therefore only opens small portions of the BBB, is one of the fundamental limitations of this technique [65-67].

Stereotactic radiation therapy

Nearly 50% of cancer patients receive ionizing radiation as part of their treatment, which is one of the main ways that radiation therapy is used to treat various cancer types. Depending on the type of tumor, its location, and the radiosensitivity of the cancer cells, several radiation therapies are applied. Radiation treatment causes the tumor cells' DNA to be damaged by directing its energy into the tumor location, which causes the tumor cells to undergo apoptosis [68-70]. Regrettably, because of the way ionizing radiation works, it may also break neighboring tissues' DNA, which can harm the brain's glial, neuronal, and vascular cells. This is why ionizing

radiation is sometimes associated with negative effects. But since oligodendrocytes and endothelial cells react to radiation, ionizing radiation may be applied precisely and carefully to intentionally harm tissue and raise the permeability of the blood-brain barrier. High radiation doses have been demonstrated to cause BBB permeability, changes in the morphology of tight junctions, a decrease in cell density, and the development of actin stress fibers in cerebral endothelial cells in healthy brain regions in both *in vitro* and *in vivo* studies [71-73]. Despite the encouraging results of these trials, there is still uncertainty regarding the best dosage (BBB permeability can be observed at dosages between 0.1Gy and 20Gy), the therapeutic window, and the method's adverse effects, which include oedema. Radiation treatment has garnered interest because it may be used with nanoparticle technology for targeted therapeutic delivery to the tumor location and immunotherapy [74].

Electric field modulation

Electric field modulation has been employed in different disciplines of medicine, most notably as a unique therapeutic approach in cancer. Electric field modification has lately been renamed tumor-treating fields, and it has been employed to open the BBB for chemotherapeutic drug delivery in a technique known as electrochemotherapy. Tumor-treating fields treatment uses transducer arrays on the skin to produce low-intensity (1-3V/cm) and intermediate-frequency (100-300kHz) alternating electric fields to the tumor area. This approach generates irreversible electroporation by delivering electric pulses to the needle electrode, resulting in nonthermal focused ablation. This results in cell death owing to compromised membrane integrity [75-77]. Tumor-treating fields have been utilized successfully in preclinical studies to decrease cell growth in cancer cell lines including as human glioma, non-small-cell lung carcinoma, breast carcinoma, and animal models of glioma and melanoma, both alone and in conjunction with chemotherapeutics. There are now multiple clinical studies in the recruitment phase that are exploring tumor treatments for brain metastases in small cell lung cancer and ependymoma. Clinical trials on brain metastasis from primary lung cancer, brain cancers, and GBM have concluded, with some data suggesting that tumor-treating fields might enhance BBB permeability. Unfortunately, clinical results have been minimal, and the practicality of using electric field modulation is taxing, as devices must be worn for 20 hours each day [78-80].

Laser induced thermotherapy

Laser Induced Thermotherapy (LITT) was first described in 1990 by Kiesslin et al. [81] who proposed that laser light could be used to cause a concentrated disruption by applying a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser pulse [81]. A stereotactic device is used to implant optical fibers and provide laser light interstitially. This laser light is deposited at low power and over an extended period of time to raise the temperature of the target region. When the thermal threshold temperature of 50 °C to 80 °C is achieved, protein denaturation and irreversible tissue coagulation ensue, resulting in lasting tissue damage [82,83]. Lower temperatures of 43 °C to 45 °C for more than 10 minutes will make cancer cells more susceptible to chemotherapy and radiation therapy. Laser treatment has been used in conjunction with tumor-specific photosensitizers such as the prodrug 5-aminolevulinic acid (5-ALA). 5-ALA has been used to treat gliomas because of its tumor selectivity and quick systemic elimination [84,85]. 5-ALA-laser combo therapy quickly breaks the BBB by creating and increasing endothelial gaps. LITT, like FUS, can be utilized in concert with nanotechnologies to direct medication delivery. In 2011, Choi [82] demonstrated that a near-infrared ultrashort pulsed laser, when combined with big molecules such as nanoparticles and genetically modified viruses, may permeate the BBB. LITT has been proven preclinically to improve survival in a GBM model [86,87].

Conclusion

The BBB is a distinct and complicated system that poses a considerable barrier to successful medication transport to the brain for the treatment of brain tumours [88]. The future paths of enhancing medication penetration into the brain for treating brain cancers are heavily reliant on technical improvements. Understanding of the BBB/BTB's significance during tumor growth and therapy has increased as more is learned about its cellular, molecular, and cancer subtype-specific properties [89]. These findings underscore the need of optimizing and defining tumour-specific treatment windows in order to break down CNS barriers and maximize medication effectiveness in the CNS while minimizing negative effects. Combining techniques for improving anticancer drug penetration across the BBB/BTB with indicators of BBB integrity may result in better therapeutic delivery and treatment results. Furthermore, clinical studies for adults and children are critical to the further development of these approaches. The development of a safe and effective strategy of bypassing the BBB for clinical usage in the treatment of brain tumors is urgently needed, and it has the potential to significantly alter the course of brain tumor therapy.

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