EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES (EEJBS)
ISSN: 2992-4138 ©EEJBS Publications
Volume 6 Issue 2 2025

Crossing Biological Barriers: Nanoscale Strategies for Enhanced Drug Delivery in Brain Tumors

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ABSTRACT

Brain tumors remain among the most challenging malignancies to treat due to the presence of complex biological barriers, particularly the blood-brain barrier (BBB) and blood-tumor barrier (BTB), which restrict the entry of therapeutic agents. Traditional chemotherapies often fail to achieve adequate drug concentrations at the tumor site, resulting in suboptimal therapeutic outcomes and systemic toxicity. Nanoscale drug delivery systems have emerged as promising tools to overcome these limitations by enhancing drug solubility, stability, and site-specific delivery. This review explores the physiological and structural challenges posed by the BBB and BTB and highlights the latest advancements in nanotechnology-based strategies designed to surmount these barriers. Key nanocarrier platforms, including liposomes, polymeric nanoparticles, dendrimers, and exosomes, are critically examined for their potential in targeting brain tumors. Furthermore, this review discusses active and passive targeting mechanisms, stimuli-responsive delivery systems, and the integration of theranostics for simultaneous imaging and therapy. Finally, the review considers clinical translation challenges and future perspectives for nanoscale strategies in neuro-oncology.

Keywords: Blood-brain barrier, Brain tumors, Nanocarriers, Drug delivery, Targeted therapy

INTRODUCTION

Brain tumors, whether primary (originating in the brain) or metastatic (originating elsewhere and spreading to the brain), remain among the most devastating forms of cancer[1]. Despite progress in oncology, these tumors are associated with high morbidity and mortality due to the unique challenges presented by the central nervous system (CNS) environment. A primary barrier to effective therapy is the presence of tightly regulated physiological barriers, particularly the blood-brain barrier (BBB), which acts as a selective shield between systemic circulation and the brain[2, 3]. This complex structure comprises endothelial cells with tight junctions, supported by pericytes, astrocytic end-feet, and a basement membrane. While essential for protecting the brain from toxins and pathogens, the BBB also inadvertently hinders the entry of many therapeutic agents, including up to 98% of small-molecule drugs and nearly all macromolecules, thus complicating drug delivery strategies for brain tumors[3–5].

The blood-tumor barrier (BTB), which forms in tumor-affected regions, is typically more permeable than the intact BBB due to abnormal angiogenesis and leaky vasculature. However, this permeability is often inconsistent and heterogeneous, varying with tumor subtype, grade, and anatomical location[6, 7]. This irregularity leads to uneven drug distribution, making it difficult to achieve therapeutic concentrations across the entire tumor mass and contributing to therapeutic failure and tumor relapse. As a result, conventional treatment strategies such as surgical resection, radiation therapy, and systemic chemotherapy have shown limited efficacy, especially in infiltrative or inoperable tumors such as glioblastoma multiforme[8, 9].

In response to these challenges, nanotechnology has emerged as a promising platform for improving drug delivery across the BBB and BTB. Nanocarriers—engineered particles typically ranging from 1 to 200 nanometers—are being developed to exploit both passive and active targeting mechanisms to enhance therapeutic delivery[10]. Passive targeting takes advantage of the enhanced permeability and retention (EPR) effect in tumor vasculature, while active targeting employs ligands or antibodies that recognize tumor-specific markers to enhance binding and uptake by tumor cells[11, 12]. These strategies can improve the pharmacokinetic and pharmacodynamic profiles of anticancer drugs, increase their accumulation within the tumor microenvironment, and reduce off-target toxicity in healthy tissues[13].

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Furthermore, functionalized nanocarriers can be designed to respond to specific stimuli—such as pH, enzymes, or temperature—within the tumor milieu, triggering controlled and localized drug release[14, 15]. Innovations in nanomedicine also include biomimetic systems that cloak nanoparticles in cell membranes to evade immune detection and increase circulation time. Collectively, these advances are shifting the paradigm of brain tumor therapy from systemic and non-specific approaches to precision-guided, targeted interventions[14, 16]. This review looks into the multifactorial barriers that hinder therapeutic delivery in brain tumors and critically assesses the array of nanoscale strategies being developed to circumvent these barriers. By highlighting recent breakthroughs and evaluating current limitations, we aim to provide an integrative overview of how nanomedicine can be leveraged for precision neuro-oncology, paving the way for improved treatment outcomes and personalized therapeutic regimens.

2. The Challenge of Biological Barriers in Brain Tumor Therapy

2.1 The Blood-Brain Barrier (BBB): The blood-brain barrier (BBB) represents a highly specialized and tightly regulated vascular interface that separates the systemic circulation from the central nervous system (CNS)[17]. This barrier is composed primarily of non-fenestrated endothelial cells that are interconnected by tight junctions, creating a physical blockade that strictly limits paracellular transport. Supporting this structural integrity are pericytes embedded in the basement membrane, astrocytic end-feet enveloping the capillaries, and various transporters and enzymes that regulate molecular trafficking[18]. The primary physiological role of the BBB is to maintain CNS homeostasis by selectively permitting the passage of essential nutrients while preventing the entry of harmful substances, including pathogens, toxins, and xenobiotics[19].

However, in the context of brain tumor therapy, the very features that make the BBB protective also make it a formidable obstacle[20]. The barrier restricts nearly all large therapeutic molecules and up to 98% of small-molecule drugs from entering the brain parenchyma. Even promising chemotherapeutic agents with demonstrated efficacy against tumor cells in vitro often fail in vivo due to inadequate penetration across the BBB[21]. Moreover, active efflux transporters such as P-glycoprotein and multidrug resistance proteins further reduce drug accumulation by actively pumping therapeutic agents out of the brain endothelial cells back into the bloodstream[22].

In the setting of malignant brain tumors, the integrity of the BBB can be partially disrupted due to tumor-induced angiogenesis and inflammatory responses. Nevertheless, this disruption is often limited and inconsistent, failing to provide sufficient permeability across the entire tumor mass[23]. Additionally, the surrounding normal brain tissue maintains an intact BBB, protecting areas where infiltrative tumor cells may reside, thus shielding them from systemic therapies[23]. As a result, the BBB remains a critical bottleneck in the successful treatment of brain tumors, necessitating the development of innovative strategies to enhance drug penetration without compromising overall CNS function[24, 25].

2.2 The Blood-Tumor Barrier (BTB)

While the BBB presents a major hurdle in healthy brain tissue, brain tumors themselves often induce the formation of a blood-tumor barrier (BTB), which arises due to pathological neovascularization and vascular remodeling[26]. Unlike the tight and continuous structure of the BBB, the BTB is characterized by leaky, irregular vasculature with disrupted tight junctions and increased fenestrations[27]. This leaky nature has led to the idea that the BTB might be exploited for enhanced drug delivery through passive diffusion or the enhanced permeability and retention (EPR) effect. However, this apparent advantage is often negated by the heterogeneous nature of BTB permeability. Studies have shown that drug permeability within tumors varies significantly depending on tumor type, grade, and intratumoral location[28, 29]. For instance, the core of a glioblastoma may demonstrate relatively high permeability, while the infiltrative margins exhibit much lower permeability due to retained BBB features. This spatial inconsistency results in uneven drug distribution, creating sanctuaries where tumor cells can evade therapy and eventually lead to recurrence.

Furthermore, the abnormal architecture of tumor blood vessels within the BTB contributes to high interstitial fluid pressure, sluggish blood flow, and compromised lymphatic drainage, all of which impair effective drug transport and retention[30]. These physiological aberrations also affect nanoparticle distribution, potentially limiting the therapeutic window. Additionally, the BTB is influenced by dynamic factors such as hypoxia, inflammation, and immune cell infiltration, further complicating drug delivery[30].

The variability of the BTB underscores the necessity for drug delivery systems that can adapt to these spatial and temporal inconsistencies. Advanced nanocarrier platforms that incorporate tumor-specific ligands, responsiveness to tumor microenvironmental stimuli (e.g., acidic pH, proteolytic enzymes), and the ability to penetrate deep into tumor tissue are currently under investigation[31]. A detailed understanding of the BTB's biophysical and biochemical properties is essential for the rational design of such systems[31]. Therefore, overcoming the challenges posed by both the BBB and the BTB requires a multifaceted approach integrating nanotechnology, molecular targeting, and systems biology for improved therapeutic success in brain tumor management.

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3. Nanoscale Drug Delivery Platforms

3.1 Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core[32–34]. Their structure allows for the simultaneous encapsulation of both hydrophilic drugs (within the aqueous interior) and lipophilic drugs (within the lipid bilayer). Due to their biocompatibility and ability to reduce systemic toxicity, liposomes are widely used in nanomedicine[35–37]. The surface of liposomes can be modified through PEGylation, adding polyethylene glycol chains to improve circulation time by reducing opsonization and uptake by the mononuclear phagocyte system (MPS)[38]. Furthermore, liposomes can be functionalized with targeting moieties such as transferrin, folic acid, or antibodies to facilitate receptor-mediated transport across the blood-brain barrier (BBB). These targeted liposomes can enhance drug accumulation in brain tumor tissues through active transport mechanisms. Clinically approved formulations like Doxil have paved the way for newer liposomal systems undergoing evaluation for glioblastoma, offering promise for more effective and less toxic brain cancer therapies.

3.2 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are solid colloidal particles typically ranging from 10 to 1000 nanometers in size and are fabricated from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG)-based copolymers[39–42]. These nanoparticles offer several advantages, including the ability to fine-tune drug release profiles and surface properties. PNPs can encapsulate a variety of therapeutic agents and release them in a controlled manner, either through passive diffusion or environmental stimuli like pH changes or enzymatic degradation. In the context of brain tumor therapy, their size and surface chemistry can be optimized to enhance penetration across the BBB. Moreover, their surfaces can be functionalized with ligands to actively target tumor-associated receptors, improving specificity and reducing off-target effects[40]. Their excellent biocompatibility, low toxicity, and ease of large-scale production make polymeric nanoparticles promising candidates for clinical translation in the treatment of gliomas and other central nervous system malignancies.

3.3 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules that exhibit a tree-like architecture with multiple generations extending from a central core[43]. This unique structural design offers abundant terminal functional groups for drug conjugation, surface modification, or targeting ligand attachment. Dendrimers such as poly(amidoamine) (PAMAM) are widely explored for drug delivery because they can encapsulate therapeutic molecules within their interior cavities or chemically attach them to surface groups[44]. Their nanometric size and uniformity make them suitable for crossing the BBB, especially when further functionalized with polyethylene glycol (PEG), antibodies, or peptides[45]. These modifications improve circulation time and targeting specificity, minimizing off-target accumulation. Dendrimers are also capable of theranostic applications, combining therapy and diagnostics by co-delivering imaging agents and drugs in a single platform[45]. Their highly controlled architecture allows for precise engineering, offering versatility in developing multifunctional nanocarriers tailored for personalized treatment of brain tumors, including glioblastoma and metastatic brain lesions.

3.4 Inorganic and Hybrid Nanoparticles: Inorganic and hybrid nanoparticles integrate metal or mineral components with organic materials to exploit their unique physical and chemical properties for drug delivery and imaging[46, 47]. Examples include gold nanoparticles (AuNPs), which exhibit strong surface plasmon resonance useful in photothermal therapy; iron oxide nanoparticles, which provide contrast in magnetic resonance imaging (MRI) and magnetic targeting; and mesoporous silica nanoparticles (MSNs), which offer high surface area and tunable pore sizes for drug loading[46, 48, 49]. These nanoparticles can be further hybridized with polymers or lipids to improve biocompatibility and functionalization potential. In brain tumor therapy, these platforms are explored for targeted delivery and real-time imaging to guide surgical resection or monitor therapeutic efficacy[50]. However, while their multifunctionality is attractive, concerns remain about their long-term safety, biodegradability, and accumulation in tissues. Thorough investigations into their pharmacokinetics, clearance, and toxicity profiles are essential before they can be safely integrated into routine clinical applications for central nervous system cancers.

3.5 Extracellular Vesicles and Exosomes: Extracellular vesicles (EVs), particularly exosomes, are nanosized (30–150 nm) lipid bilayer-enclosed particles naturally secreted by cells for intercellular communication[51–53]. They transport proteins, lipids, and nucleic acids, and possess innate capabilities to traverse biological barriers such as the BBB. Their endogenous origin provides superior biocompatibility, low immunogenicity, and extended circulation, making them attractive vehicles for drug delivery. Exosomes can be isolated from various biological fluids and engineered to carry therapeutic agents, including small molecules, siRNAs, and CRISPR components. Surface modifications, such as ligand conjugation or genetic engineering of parental cells, can enhance their targeting to tumor tissues. In brain tumor applications, engineered exosomes are being explored for delivering chemotherapeutics or genetic payloads to glioblastoma cells.[54–56] Their capacity to mimic

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natural cellular communication mechanisms offers a promising, minimally invasive approach to personalized nanomedicine. However, challenges such as scalable production, efficient drug loading, and standardization of isolation techniques need to be addressed for clinical translation.

4. Mechanisms for Crossing the BBB

4.1 Passive Targeting via EPR Effect: The Enhanced Permeability and Retention (EPR) effect refers to the tendency of nanoparticles to accumulate in tumor tissues due to the leaky vasculature and impaired lymphatic drainage typical of many tumors[57]. This passive targeting mechanism has been widely used in solid tumor therapy to enhance drug concentration at the tumor site. However, the EPR effect in brain tumors is relatively limited compared to peripheral tumors[57, 58]. The presence of the highly selective BBB restricts passive diffusion of most macromolecules and nanocarriers. Nonetheless, in glioblastoma and other high-grade brain tumors, regions of the BBB may become partially disrupted, permitting some degree of nanoparticle accumulation via the EPR effect[58]. Despite this, the heterogeneous and incomplete nature of BBB disruption poses significant limitations for relying solely on passive targeting. As a result, passive accumulation through the EPR effect often needs to be supplemented with active targeting strategies or stimuli-responsive systems to achieve therapeutic concentrations in brain tumor tissues.

4.2 Active Targeting Strategies: Active targeting enhances nanoparticle delivery across the BBB and into tumor cells by functionalizing the nanocarrier surface with ligands that bind specific receptors on endothelial or tumor cells[59]. These ligands include transferrin, lactoferrin, folic acid, peptides (e.g., RGD), and antibodies against overexpressed surface markers. Upon binding to their receptors, the nanoparticle-ligand complex is internalized via receptor-mediated endocytosis or transcytosis, allowing the therapeutic payload to cross the BBB efficiently. For example, transferrin receptor-targeting nanoparticles have shown promise in preclinical models of glioma by improving drug accumulation in the brain. Similarly, insulin or integrin-targeted systems exploit naturally occurring transport mechanisms to ferry drugs across endothelial barriers[60]. This strategy not only increases specificity and uptake but also minimizes off-target side effects and systemic toxicity. Active targeting remains a cornerstone of precision nanomedicine, particularly for brain tumors where traditional drug delivery methods are hindered by the restrictive and protective nature of the BBB.

4.3 Stimuli-Responsive Delivery Systems: Stimuli-responsive delivery systems are intelligent nanocarriers designed to release their therapeutic cargo in response to specific internal or external triggers[14, 61, 62]. In the context of brain tumors, internal stimuli such as acidic pH, elevated redox potential, overexpressed enzymes, or hypoxia within the tumor microenvironment can be exploited for controlled drug release. For example, pH-sensitive nanoparticles can remain stable in the bloodstream (pH ~7.4) but undergo structural changes in the acidic tumor milieu (pH ~6.5–6.8), triggering drug release specifically at the tumor site. Similarly, redox-sensitive systems can respond to high intracellular glutathione concentrations in cancer cells to release chemotherapeutics[63]. External stimuli such as heat, light, or magnetic fields can also be applied to trigger release from thermosensitive, photosensitive, or magnetically-responsive carriers. These smart delivery systems enhance therapeutic efficacy while reducing off-target toxicity. Their integration into brain tumor treatment strategies holds great promise for overcoming the challenges of delivering potent agents across the BBB with spatial and temporal precision.

5. Theranostic Nanomedicine and Imaging-Guided Therapy

Theranostic nanoparticles represent a cutting-edge advancement in nanomedicine by integrating diagnostic and therapeutic functionalities into a single platform[64, 65]. This dual capability allows for simultaneous disease imaging and targeted drug delivery, revolutionizing the way clinicians monitor and treat diseases, particularly cancer. By enabling real-time tracking of the biodistribution of therapeutic agents and assessment of treatment efficacy, theranostic nanoparticles can significantly enhance treatment personalization and responsiveness.

Several classes of nanoparticles have been explored for theranostic applications. Magnetic nanoparticles, such as superparamagnetic iron oxide nanoparticles (SPIONs), serve as contrast agents in magnetic resonance imaging (MRI) while also being capable of delivering drugs or mediating hyperthermia therapy[66, 67]. Quantum dots, owing to their unique optical properties, are used in fluorescence imaging and can be conjugated with therapeutic molecules for targeted delivery. Gold nanoshells and nanorods, known for their tunable surface plasmon resonance, can absorb near-infrared light and convert it into heat, enabling both photothermal therapy and imaging.

The integration of these imaging modalities with targeted therapy helps improve treatment precision by ensuring drugs are delivered specifically to diseased tissues while minimizing off-target effects. This reduces systemic toxicity and enhances therapeutic outcomes. Furthermore, real-time imaging allows clinicians to assess whether the therapeutic agent has reached its intended target and how the disease is responding to treatment[68]. If necessary, treatment regimens can be rapidly adjusted, providing a level of adaptability not possible with traditional methods.

In addition to oncology, theranostic nanoparticles are being studied for use in cardiovascular diseases, neurodegenerative disorders, and infectious diseases[69]. As research progresses, improvements in

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biocompatibility, targeting specificity, and imaging sensitivity will continue to drive the clinical translation of theranostic nanotechnologies, making them a vital component of future precision medicine strategies.

6. Clinical Translation and Challenges

Despite promising preclinical results, clinical translation of nanomedicine for brain tumors faces significant challenges. These include manufacturing scale-up, regulatory hurdles, reproducibility, immune response, and long-term safety. Furthermore, inter-patient variability in BBB integrity and tumor biology complicates treatment standardization. Clinical trials such as those involving nanoliposomal irinotecan or transferrin-modified nanoparticles have shown potential but require further validation.

7. Future Perspectives

The future of nanoscale brain tumor therapy lies in multi-functional, smart nanoparticles that integrate targeting, stimuli-responsiveness, and real-time feedback. Advances in artificial intelligence, microfluidic screening models, and precision medicine will accelerate the optimization of nanoparticle formulations. Personalized nanomedicine approaches, leveraging patient-specific tumor profiles, hold the potential to revolutionize neuro-oncology and overcome the current limitations of conventional treatments.

CONCLUSION

Crossing the BBB remains one of the greatest hurdles in brain tumor therapy. Nanoscale drug delivery systems offer a promising avenue for circumventing this challenge by enhancing the delivery, specificity, and safety of therapeutic agents. Continued interdisciplinary collaboration between nanotechnology, neuroscience, oncology, and pharmacology will be critical for translating these innovative platforms into effective clinical therapies for brain tumor patients.

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Obwendo N. J. Crossing Biological Barriers: Nanoscale Strategies for Enhanced Drug Delivery in Brain Tumors. EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES, 6(2):78-85.

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