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Nanobiotechnology-based delivery strategies: New frontiers in brain tumor targeted therapies

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ABSTRACT

Despite recent technological advancements and promising preclinical experiments, brain tumor patients are still met with limited treatment options. Some of the barriers to clinical improvements include the systemic toxicity of cytotoxic compounds, the impedance of the blood brain barrier (BBB), and the lack of therapeutic agents that can selectively target the intracranial tumor environment. To overcome such barriers, a number of chemotherapeutic agents and nucleic acid-based therapies are rapidly being synthesized and tested as new brain tumor-targeted delivery strategies. Novel carriers include liposomal and polymeric nanoparticles, wafers, microchips, microparticle-based nanoplatforms and cells-based vectors. Strong preclinical results suggest that these nanotechnologies are set to transform the therapeutic paradigm for brain tumor treatment. In addition to new tumoricidal agents, parallel work is also being conducted on the BBB front. Preclinical testing of chemical and physical modulation strategies is yielding improved intracranial concentrations. New diagnostic and therapeutic imaging techniques, such as high-intensity focused ultrasound and MRI-guided focused ultrasound, are being used to modulate the BBB in a more precise and non-invasive manner. This review details some of the tremendous advances that are being explored in current brain tumor targeted therapies, including local implant development, nanobiotechnology-based delivery strategies, and techniques of BBB manipulation.

1. Introduction

Glioblastoma (GB) is the most common and aggressive primary brain tumor, and remains one of the most lethal cancers in humans with a median survival after maximal therapy of less than 2 years after initial diagnosis [1–3]. The nature of the tumor, such as high invasiveness, a high proliferative index, immunologic escape, genetic heterogeneity, and genetic instability as well as the unique intracranial environment and the physio-anatomic barriers between the brain and the tumor [4] have limited the efficacy of standard chemotherapeutic agents.

One of the major obstacles in the development of agents for the treatment of central nervous system (CNS) diseases is formulating a therapeutically relevant concentration of a compound that can effectively cross the blood brain barrier (BBB). Antitumor molecules need to circumvent specific brain- and tumor-related physio-anatomical barriers, including: i) the neuro-vascular unit (NVU) which regulates the trafficking of substances between the blood stream and the CNS [4]; ii) the extra-cellular space (ECS) that affects the flow of nutrients, metabolites, cytokines, neurotransmitters, and other molecules between tumors and brain tissue [4]; and iii) the enhanced permeability and retention effect (EPR effect) which, though directly proportional to tumor growth, is significantly altered in the intracranial microenvironment [5].

Strategies to circumvent the impermeability of the BBB have followed both local and systemic routes. The first local delivery strategy to be used clinically was interstitial chemotherapy, which employed a polymeric wafer, Gliadel®, to bypass the BBB and deliver a sustained release of the chemotherapeutic agent carmustine directly at the site of tumor resection. The development and subsequent FDA approval of Gliadel® was a hallmark of both technology and translational medicine. Gliadel® increased the median survival for patients with brain tumors after tumor resection from 15 months with radiation and oral chemotherapy to 21.3 months [1]. The approval of these drugs filled a 25 year gap when no new brain tumor therapies were developed and not much hope was offered to brain tumor patients. Gliadel® also opened the door for other agents to be tested at the local intracranial level and was the beginning of further advancements combining technology and innovation for clinical benefit.

The biomedical revolution of recent years has opened new therapeutic avenues for the treatment of brain tumors using both local and systemic routes of administration depending on the physical and chemical features of the nano- and bio-vectors used. Promising strategies have included the use of different families of liposomal and polymeric nanoparticles, thermosensitive gels, dendrimers, as well as immunocytes and stem cells used as "Trojan horses" due to their innate tumor homing capacity. Among the most exciting is the introduction of

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nanomedicine-based approaches to tumor-targeted drug delivery. These nanoparticles can enter the brain tumor through the endothelial gaps on the microvessels of brain tumors by taking advantage of the glioma EPR effect and/or their ligand- and receptor-coated surfaces [6]. These nanostrategies have also been combined with classical methods to cross the BBB as well as novel techniques, such as ultrasound (US) and magnetic resonance imaging (MRI), thereby developing new scenarios in CNS drug-delivery strategies [7]. Another biomedical innovation is the use of immune cells and stem cells for gene delivery to the brain. In this review we detail current efforts focused on the role of new nano- and bio-technologies to optimize the delivery of therapeutic drugs and genes as well as repurposing theranostic techniques such as US, MRI and high intensity focused ultrasound (HIFU) to facilitate the penetration of these vectors through the BBB for brain tumor targeted therapy.

2. Local implant development

Despite the number of new chemotherapeutic agents produced every year, as well as the prospects of personalized medicine and nucleic acid-based therapies offered by recent advances in genomics, all drug delivery approaches face similar challenges in the intracranial environment. These challenges include crossing the blood–brain barrier (BBB) to reach the tumor efficiently and selectively, and successfully achieving the balance between maximizing antitumor efficacy and minimizing risks of toxicity. To ensure that therapies are kept within the beneficial side of this equation, considerable effort has been expended to improve strategies of tumor-targeting drug delivery. These methods permit the highest drug concentration at the tumor site with the lowest risks of systemic toxicity. A variety of technologies has been modeled in a similar manner to wafer implants, ranging from tablets, liquids and injectable gels, to sophisticated systems utilizing bioengineered products to deliver different categories of drugs for brain tumor treatment (Table 1). Many of these products use polymer-based drug delivery systems with each technology offering unique advantages to drug delivery and, insofar as they enhance BBB penetration and help to specifically target brain tumor cells [8,9], most should merit inclusion in the armamentarium for the treatment of malignant brain tumors. However, local drug delivery has attracted concerns due to the risks to healthy brain tissue, the need of a surgical procedure for implantation, and the limitations associated with either a single administration of therapy or controlled drug release over time [10–13].

2.1. Polymeric wafers

Of the many biomaterial drug-polymer devices developed to date, the Food and Drug Administration (FDA) and the National Institute for Health and Clinical Excellence (NICE) have only approved the use of polymeric wafers (Gliadel®) for local chemotherapy in the treatment of primary and recurrent malignant glioma [14,15]. These wafers, which are neurosurgically implanted at the time of tumor resection, gradually release the chemotherapeutic agent carmustine, which then diffuses into the surrounding brain and targets the residual cancer cells that have infiltrated the brain tissue. The polymer used in patients is composed of polyanhydride poly[1,3-bis (carboxyphenoxy) propane-*co*-sebacic-acid] (PCPP:SA) and incorporates the chemotherapeutic drug, carmustine, or BCNU [16,17].

Preclinical studies of BCNU incorporated into the polymeric wafer, BCNU:pCPP:SA, included cytotoxicity studies using rodent and human glioma and gliosarcoma cells and extensive release kinetic analyses in vitro [18]. In vivo safety, biodistribution and efficacy studies were then conducted in rodents and non-human primates to confirm the utility of the intracranially implanted wafer [19,20]. A Phase I trial was conducted demonstrating the safety of the wafer and establishing the dose at which Gliadel® would be delivered [16]. In 1996, the FDA approved Gliadel® for use in patients with recurrent glioblastoma as an adjunct to surgery. In 2003, Gliadel® was approved for use in patients with newly diagnosed high grade malignant glioma as an adjunct to surgery and radiation and, in 2004, Medicare created a new diagnosis-related group, or DRG, to allow for Gliadel® to be prescribed for patients. Combining Gliadel®, radiation and oral Temozolomide has since led to an increase in the median survival for patients with malignant glioma, ranging from 18 to 21 months [1]. Multiple clinical reports have verified these findings and a recent meta-analysis supported the conclusion that Gliadel® has played a significant role in improving the survival for patients with newly diagnosed glioblastomas [21]. Gliadel® became a pioneer for intra-cavity drug delivery and still represents an important yardstick for intracranial delivery approaches for brain tumor therapy.

Other preclinical local delivery approaches have included various polymeric formulations, including ethylene-vinyl acetate copolymer (EVAc), fatty acid dimer-sebacic acid copolymer (FAD:SA), poly(lactide-*co*-glycolide) polymers, and polyphosphoester polymer p(DAPG-EOP) in the form of microspheres at 10% (w/w) for the sustained release of paclitaxel (Paclimer®) [22]. These polymers differ in multiple ways, including the variety of drugs that can successfully be incorporated and reliably delivered, subsequent release kinetics and overall stability. Preclinical studies show that several drugs, otherwise limited by systemic toxicity or poor brain penetration, report higher survival in experimental glioma models when delivered intracranially by polymeric wafers than the same drug delivered by systemic administration. Among them are temozolomide [23], taxol [22,24], minocycline [25], doxorubicin [26], rapamycin [27], camptothecin [28], carboplatin [29], as well as many others [28,30–34].

2.2. Thermosensitive and thermodependent gels

Thermosensitive hydrogels have recently gained increased interest. These gels can be used to deliver hydrophilic and hydrophobic compounds in their free state, as well as nanoparticle-encapsulated compounds [35]. Injectable thermosensitive hydrogels with lower sol-gel transition temperatures, in which the solution gradually changes into the formation of a gel at physiological temperatures, hold great potential as they can be injected directly into the tumor cavity. Dhillon et al. and Rahman et al. developed a novel temperature-sensitive and

Table 1
Categories of compounds delivered via local implants.

Categories	Compounds	Type of implants
Alkylating agent	BCNU, cyclophosphamide, temozolomide, carboplatin	Polymeric wafers
Glycolytic inhibitor	3-Bromopyruvate, dichloroacetate	Polymeric wafers
Topoisomerase Inhibitor	Camptothecin, *Etoposide*	Polymeric wafers and matrices
Antibiotic	Doxorubicin, minocycline, lactacystin	Polymeric wafers
Plant alkaloid	Docetaxel	Polymeric wafers
Antineoplastic	Epirubicin	Polymeric wafers
Anti-angiogenetic agent	Endostatin: synthetic endostatin fragment (EF) and Fc-endostatin	Polymeric wafers
Plant alkaloid	Paclitaxel	Polymer matrix
mTOR inhibitor	Rapamycin	Polymeric wafers
Immune modulator	Interleukin-2 (IL-2)	Polymeric matrices and wafers

biodegradable formulation based on blended poly(lactic-*co*-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG) microparticles [36,37]. This technology was used successfully to deliver an osteogenic growth factor for bone repair in a murine calvarial defect model [38]. The PLGA/PEG microparticle-based matrices bring several advantages to local drug delivery including: (i) the physical capability to be molded into any shape or size, such as the irregularly shaped surgical resection cavity walls; (ii) the capability to incorporate and release multiple drugs, thus increasing the flexibility of treatment offered to the clinician and the patient; and (iii) a sustained drug release of 1–3 weeks, allowing for oncological treatment in the interval before the start of post-operative chemo/radiotherapy [39]. The microparticles have the consistency of free-flowing powder at room temperature and then create a paste when mixed with a saline-based carrier solution. The formulation can be injected or pasted at room temperature until it gradually solidifies (sinters) into a solid, porous matrix at body temperature. Importantly, PLGA microspheres degrade gradually and have a good biocompatibility profile in brain tissue [40]. This formulation was shown to be clinically compatible with radiotherapy and magnetic resonance imaging/computerized tomography (MRI/CT) scanning modalities. Researchers have successfully shown sustained in vitro release of trichostatin A (TSA), etoposide (ETOP) and methotrexate (MTX) from this formulation [39]. Etoposide was delivered via this self-sintering paste and was found to be well tolerated and have anti-tumor and anti-angiogenic effects in a murine glioblastoma model [41].

Camptothecin, a quinolone alkaloid that inhibits topoisomerase I, has been shown to be an effective cytotoxic agent for brain tumor therapy [42]. Due to its low solubility, its efficacy was greatly enhanced by polymeric delivery. Camptothecin, when incorporated into CPP:SA and implanted intracranially, showed a statistically significant and impressive improvement in survival in the 9 L rodent gliosarcoma model in vivo [28,31]. Similarly, when delivered via a poly(lactic-*co*-glycolic acid) (PLGA) microsphere-containing thermoreversible gelation polymer (TGP) (drug/PLGA/TGP) formulation, survival was markedly increased in the C6 rodent glioma model [43].

Paclitaxel, an antitumor compound that demonstrates strong cytotoxic properties with malignant tumors by enhancing the polymerization of tubulin has been shown to be an effective chemotherapeutic agent in preclinical studies [22]. There have been multiple polymeric formulations developed to deliver paclitaxel and its synthetic analog docetaxol [22,24]. A thermosensitive triblock copolymer (PLGA–PEG–PLGA), water soluble at 2–15 °C which turns into a viscous gel at body temperature [44], was loaded with paclitaxel and termed OncoGel. It is a depot formulation of paclitaxel which, after a single administration, is designed for sustained paclitaxel delivery over approximately 6 weeks. Pre-clinical and early clinical investigations demonstrated OncoGel's ability to deliver paclitaxel to esophageal and brain tumor tissue via intralesional injection into the tumor cavity following resection, with an acceptable safety profile and moderate increase in survival in a rat gliosarcoma model [45,46]. The Phase I clinical trial with OncoGel administered directly into solid tumors showed that it was well tolerated and paclitaxel remained localized at the injection site, thus minimizing systemic exposure [47]. However, the Phase I/II escalation dose trial was terminated without conclusive results (NCT00479765) and the gel is not currently in production.

An advance of the same concept comes from the nanotechnologies, as shown by Lee et al. [35]. Recent developments include a paclitaxel-loaded injectable in situ-forming gel using MPEG-PCL copolymer gels. Liquid at room temperature, this formulation turns gelatinous at body temperature and has shown a sustained release for 2 weeks in vitro. This paclitaxel injectable depot has significantly improved antitumor efficacy compared to Taxol, saline (control), and placebo gel in a B16F10 tumor-bearing mouse model upon intratumoral injection [48]. These positive results have encouraged further research into the development of alternatives to Cremophor EL-based paclitaxel, due to its risks of hypersensitivity reaction and paclitaxel precipitation in aqueous infusions. One Cremophor-free alternative is using solid lipid nanoparticles (SLNs), which comprise of trimyristin as solid core and egg phosphatidylcholine (ePC) plus distearoylphosphatidyl-ethanolamine-N-poly-(ethylene glycol) 2000 (PEG2000–PE) as stabilizers. They are loaded with 6% paclitaxel, and have been found comparable in toxicity to Cremophor. Another alternative is the Cremophor EL-free paclitaxel (CF-PTX) formulation, which consists of soya phosphatidylcholine and biosurfactant sodium deoxycholate. CF-PTX was found to be comparable to Cremophor EL in drug-loading capacity (6 mg/ml), but superior in vivo performance and cytotoxicity profiles [35].

2.3. Microchips–microelectromechanical systems and passive microchips

Microchips – miniaturized depot devices – are a viable method for controlling drug delivery to brain tumors, and have the potential to achieve a broad aggregate distribution profile [49,50]. These devices are capable of delivering multiple drugs with independent drug release profiles following a single implantation procedure. The advantages of the microchip as an intracranial drug delivery device are that the drugs remain intact in the microchip for much longer than in the polymer with no drug–polymer interactions [51]; they can allow for a larger payload of drug than the drug–polymer mix; and they can be programmed to deliver a particular controlled drug release pattern as compared to polymers, which, especially in acidic tumor environments, degrade very rapidly [51]. Two types of microchips, microelectromechanical systems and the passive chip, have shown encouraging preclinical results in rodent flank models of glioma in the delivery of temozolomide and carmustine, two standard alkylating compounds used to treat patients with brain tumors. Both types of microchips have been miniaturized for proof of principle experiments in the rodent brain and have shown statistical increases in survival in orthotopic models of brain cancer [52]. A future application of microchip devices for intracranial chemotherapy holds tremendous potential for the treatment of malignant gliomas.

3. Nano- and bio-carriers

Nano- and bio-carriers are two of the most promising new instruments of non-invasive delivery systems (Table 2). These types of carriers can enhance the permeability of therapeutic agents across the BBB, carry intracellular drugs, and increase cargo half-life. Nanocarriers have attracted much interest in the field of cancer drug delivery on account of their proven ability to take full advantage of the enhanced permeation and retention (EPR) effect [53]. The EPR effect occurs in high-grade gliomas, where high rates of angiogenesis cause the tumor vasculature to become “leaky” [54]. Particles, between ~20 nm and ~100 nm, extravasate preferentially from tumor tissue, due to the tumor's greater vascular permeability as compared to normal tissue and are preferentially retained in the tumor tissue rather than returned to systemic circulation [55]. The physical properties of nanoparticles, such as their small size, their degree of surface coating, and their deliverability by convection enhanced delivery (CED), make them especially suited for application in brain tumor therapy. Although still in early preclinical phase testing, colloidal drug carriers, including both nanoparticles and liposomes, have shown promising features as drug carriers to brain tumors after both local and intravenous administration. The second type of non-invasive delivery vectors are biological carriers, or bio-carriers. Growth factors and inflammatory cytokines and chemokines, in particular, have shown much promise thanks to their brain tumor homing capacity. Inflammatory cytokines and chemokines tend to guide immune and stem cells directly through the BBB and toward the tumor site where they can be engineered to deliver therapeutic agents [56]. However, further trials are needed to settle existing controversies surrounding the use of autologous cells before such personalized approaches to brain tumor therapy can become a clinical reality.

Table 2
Summary of brain tumor-targeted therapy strategies using colloidal and biological carriers.

Liposomal carriers	Drug/gene	Administration route/study
Transferrin-conjugated liposomes	5-Fluorouracile	Intravenous/preclinical
Myocet®	Doxorubicin	Intravenous/Phase I–II study
Lipoplatin®	Cisplatin	Intravenous and FUS/preclinical
DaunoXome ®	Daunorubicin	Intravenous/Phase I study
DepoCyt®	Cytarabine	Intraventricular/Phase I–II study
Nanocarriers	**Drug/gene**	**Administration route/study**
PEG-PLGA nanoparticles	Paclitaxel	Intracranial/preclinical
Lecithin-containing PLGA nanoparticles	Doxorubicin	Intravenous/preclinical
Albumin-conjugated PEG-PLGA nanoparticles	Aclarubicin	Intravenous/preclinical
PLGA nanoparticles	Camptothecin	Intravenous/preclinical
PLGA nanoparticles	Dithiazanine Iodide	Convection enhanced delivery/preclinical
Transferrin-conjugated magnetic silica PLGA	Doxorubicin and Paclitaxel	Intravenous/preclinical
Angiopep-2 (ANG)-modified PLGA	Doxorubicin/EGFRsiRNA	Intravenous/preclinical
PBAE nanoparticles	HSVtk	Convection enhanced delivery/preclinical
Cells-based delivery	**Drug/gene**	**Administration route/study**
Natural killer cells	Gold nanoshells	Intravenous/preclinical
Monocytes/macrophages	HER2-receptor	Intravenous and FUS/preclinical
Mesenchymal stem cells	TRAIL/IL12-IL18-oHSV/BMP4	Intranasal/intracranial/intracardiac/preclinical
Neuronal stem cells	IFN-β and CD	Intravenous/preclinical
	CD and 5-fluorocytosine	Intracranial/safety and efficacy study

3.1. Nanocarriers

Nanoparticles can be fabricated using a wide range of different materials. Synthetic, biocompatible and hydrolytically degradable polymers such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and the copolymer poly(lactic-*co*-glycolic acid) (PLGA), chitosan, poly(beta-amino esters), and poly(amidoamines) have been used to deliver several therapeutic small macromolecules, such as proteins and nucleic acids [57]. Positively charged polymers are studied particularly for delivery of nucleic acids, because their cationic character allows them to form nanocomplexes with negatively charged DNA and RNA.

Preclinical studies in brain tumor models have shown superior efficacy of different therapeutic agents such camptothecin [58], dithiazanine iodide, doxorubicin [59], aclarubicin [60] and paclitaxel [61,62] when delivered in PLGA nanoparticle formulations compared to free drugs. Densely PEGylated PLGA nanoparticles have shown superior diffusion and efficacy profiles compared to non-PEGylated particles. Chitosan-based nanoparticles can be effectively conjugated with fluorescently-labeled chlorotoxin, which binds specifically to gliomas [63] to result in preferential accumulation in gliomas [64,65]. Glycol chitosan (GC)-based nanoparticles (CNPs) can serve as platforms to encapsulate both chemotherapeutics and siRNA. Specifically, doxorubicin and Bcl-2 siRNA-encapsulated CNPs exhibited similar in vivo biodistribution and pharmacokinetics regardless of the different physical features of DOX and Bcl-2 siRNA; both enhanced treatment in a dose-dependent manner [66]. Poly(beta-amino) esters (PBAE) polymers have been shown to be safe and effective DNA/RNA delivery vectors. Indeed, they can be engineered to exhibit cell-type specificity and to selectively transfect tumor tissue while avoiding surrounding healthy tissue. PBAE polymers can also increase tumor biodistribution when delivered via CED, rather than via direct bolus injection, and can provide significant benefit in survival when loaded with herpes simplex virus type I thymidine kinase (HSVtk) [67]. Finally another category of nanoparticle, dendrimers, has shown to be a promising carrier for brain tumor-targeted therapy. Poly(amidoamine) (PAMAM) dendrimers are branched macromolecules which have a very small hydrodynamic size compared to conventional polymeric nanoparticles or liposomes and allows for effective penetration of the blood brain tumor barrier (BBTB) [68,69]. Dendrimers can be loaded with different drugs and proteins [70]. Specifically, hydroxyl terminated generation 4 PAMAM (G4-OH PAMAM) dendrimers (4.3 nm near-neutral nanoparticle) have demonstrated favorable safety profiles in vivo [71,72]. Dendrimers also demonstrate selectivity in targeting brain tumors and uniformly diffuse and are retained in the tumor mass after intravenous injection [73]. This has been attributed to their selective uptake from tumor associated macrophages (TAMs) [73].

3.2. Liposomal carriers

Liposomes have widely been used as carrier systems for the delivery of several therapeutic agents due to their easy preparation, good biocompatibility, low toxicity, and commercial availability. Liposomal encapsulation can prolong the encapsulated compound's half-life after systemic injection while changes in size and surface modification by PEGylation can be used to further improve the compound's circulation and availability. PEGylated liposomes conjugated to mAbs against the transferrin receptor OX26 were used to specifically target the brain [74]. Transferrin conjugated liposomes were also used to deliver the anticancer drug 5-fluorouracil (5-FU), known to poorly penetrate the brain when given systemically [75]. Several liposomal anticancer drugs are available in the clinic and are in advanced stages of clinical trials for breast cancer and AIDS-related Kaposi's sarcoma [76,77]. Approved drugs include pegylated liposomal doxorubicin (Doxil/Caelyx®), non-pegylated liposomal doxorubicin (Myocet®), liposomal daunorubicin (DaunoXome®), liposomal cytarabine (DepoCyt®) and liposomal cisplatin (Lipoplatin®). DaunoXome®, after the encouraging preclinical results, has reached the Phase I safety study level, but has yet to show reduced systemic toxicity [78]. The safety of the intraventricular administration of DepoCyt® was tested in a clinical study but, despite good response in two cases, the trial was ended because of insufficient patient enrollment (Clinical trial ID no. NCT01044966). Lipoplatin® has shown promising results when conjugated with atherosclerotic plaque-specific peptide-1 (AP-1) and administrated intravenously followed by focused ultrasound (FUS) [79]. Finally, Myocet® the liposomal doxorubicin compound, has been tested extensively. Myocet® has a longer half-life and significantly less cardiotoxicity from the doxorubicin in the liposomal formulation as compared to the free doxorubicin with comparable antitumor efficacy. The promising results of Myocet® have even yielded modest clinical benefits when tested in adults with recurrent high-grade gliomas [80]. Further trials should be implemented for childhood malignancies following the recently recommended safety dosage of Myocet® in children with refractory high-grade gliomas.

3.3. Cell-based therapy

A promising strategy to bypass the BBB is the use of vectors that can enter the brain as Trojan horses following systemic administration. Multiple stem cell types have been shown to exhibit inherent tropism toward brain tumors, such as neuronal stem cells (NSCs), bone marrow stromal cells (BMSCS) and adipose tissue-derived mesenchymal stem cells (AMSCs) and immune cells [81]. Specifically, pathotropic delivery vehicles can be engineered to express therapeutic agents and can effectively target sites of malignancy [82]. In brain tumor-targeted therapies, immune cells such as natural killer (NK) cells have been shown to reach breast metastases in the brain after intravenous injection when modified to express the HER2 antigen receptor in combination with focused ultrasound [83]. However, among immune cells, macrophages seem to be the cells that play the most prominent role, as evidenced by the fact that systemically injected paramagnetic nanoparticles for MRI were ingested by endogenous macrophages and subsequently migrated and accumulated in and around tumors [84,85]. The fact that tumor-associated macrophages (TAMs) can also constitute up to a third of the tumor only strengthens the case for the use of macrophages as cell-based therapeutic delivery vehicles to brain tumors. For example, macrophages have been shown to carry gold nanoshells, photothermal agents for photothermal therapy, and infiltrate glioma spheroids successfully in vitro [86]. Stem cells have also already been widely employed as vehicles for delivering different therapeutic agents to brain tumors. They have been used to deliver suicide genes, particularly cytosine deaminase (CD) and tyrosine kinase (TK), which can be delivered either alone or in pairs [87,88]. Stem cells have also been employed to deliver cytokines, such as IL-18 [89], IL-12 [90,91], oncolytic viruses, and suicide genes delivered in combination [92,93], such as HSVtk with TRAIL [88] or CD with IFN-β [94]. The use of oncolytic viruses, in particular, holds much promise inasmuch as viruses have the ability to selectively replicate in, and kill, tumor cells while sparing healthy cells [95]. However, their therapeutic efficacy is limited since viruses are actively cleared by the host's defense mechanisms following systemic administration and viruses' diffusion has not been sufficient following intratumoral administration. To circumvent antiviral immunity [96], several studies have successfully used stem cells (SCs) as delivery vehicles for glioma therapy using oncolytic viruses alone [97–100] or in combination with chemo and radiotherapy [101]. Mesenchymal stem cells (MSCs) loaded with oncolytic herpes simplex virus (oHSV) have recently been shown to be effective and provide a significantly higher benefit in glioma-bearing mice compared to pure oHSV [102]. Despite good preclinical results, the clinical application of stem cells as carriers of brain-targeted therapy is still controversial. This controversy is due to 1) the absence of any standardized protocol for the clinical translation from in vitro cell culture to in vivo administration; 2) the general uncertainty as to the SC's behavior in vivo; and 3) the safety of the viral system needed to engineer the stem cells. The first trial in humans was recently completed and used an immortalized, clonal, expandable neural SC line. It was also the first to use neural SCs to deliver a therapeutic agent for cancer treatment. In this Phase I trial (clinical trial ID no. NCT01172964), the neural SCs were engineered to deliver the enzyme carboxylesterase (CE) into recurrent high-grade gliomas of adult patients. There, carboxylesterase should activate a systemically administered prodrug, Camptothecin-11 (CPT-11), into a powerful chemotherapeutic agent, SN-38, which should select and destroy invasive glioma cells at tumor sites while sparing normal tissues [103]. The results of this trial will help elucidate the potential clinical application of stem cell based brain tumor therapy.

4. BBB permeability modulating strategies

Many strategies have been developed to both circumvent the BBB and increase the chemotherapeutic concentration in the tumor following systemic administration. These methods, summarized below, rely heavily on understanding both the chemical and physical modulation of the BBB, including pharmaceutical BBB modification as well as the conjugation of therapeutic compounds with substances and/or vectors that can facilitate passage through the BBB. These methods have been used to improve the ability of the nanoparticles to penetrate the tumor and diffuse throughout the tumor mass. Despite some studies showing that the EPR effect can allow for tumor accumulation of particles around 100 nm via the disrupted BBTB [35], others have proven that only smaller particles (of ~20 nm or smaller) can cross the BBTB [45,48,104]. In fact, the tumor vasculature is not homogeneous [105]and remains largely intact at the tumor margins and more permeable within the bulk of the tumor. The utilization of BBB permeability modulation strategies, particularly using theranostic techniques, such as focused ultrasound and high-intensity focused ultrasound (HIFU), represents a promising combined approach for an effective and non-invasive brain tumor-targeted therapy.

4.1. Drug modifications and nano-conjugations

Owing to the presence of epithelial-like, high resistance tight junctions, and the absence of paracellular or transcellular channels within the BBB, the molecules in the circulation gain access to the brain via (i) lipid-mediated free diffusion through the BBB; (ii) transcellular transport through endothelial cells (via diffusional peptide liposome) and nanoparticles (by carrier- or adsorptive-mediated process (AMT) or receptor-mediated transport (RMT)); and (iii) enhanced drug delivery via paracellular transport between adjacent endothelial cells by chemical and physical BBB disruption [106]. Free diffusion through the BBB is limited to molecules that fit the dual criteria for lipid-mediated free diffusion, i.e., (1) MW <400 Da threshold and (2) high lipid solubility [106,107]. The addition of moieties not only increases a drug's lipophilicity, but also increases the likelihood that it will cross the BBB [108]. In addition to improved penetration, direct conjugation is also capable of enhancing the parent drug's efficacy. A conjugation of temozolomide has been accomplished by using cycloaddition reactions, in which the dien-component is obtained by coupling the amide group of the temozolomide with a tetrazine. TMZ-BioShuttle, formed by covalent chemical conjugation of temozolomide to a transmembrane transport peptide, has been reported to have better in vitro activity against some glioma cell lines at reduced dose levels, suggesting its potential to minimize systemic side effects [109]. The TMZ-BioShuttle may be able to take advantage of the AMT and the RMT [110].

Nanoparticles represent a promising vehicle to facilitate the passage across the BBB using the aforementioned transcellular mechanisms, especially via RMT. In this approach, endogenous ligands (e.g., transferrin, lactoferrin and folate) and peptidomimetic antibodies (OX26) can be attached to the outer shell of nanoparticles to allow for the utilization of the RMT systems for brain targeting [111,112]. For instance, polybutylcyanoacrylate (PBCA) polymeric nanoparticles (PBCA-NPs), when coated with polysorbate 80 (PS80), a mild inhibitor of P-glycoprotein (Pg-p), (PS80-coated PBCA-NPs) have shown penetration of the BBB. Specifically, PS80-coated PBCA-NPs loaded with doxorubicin were reported to exhibit significant anti-tumor efficacy in a rat glioma model, suggesting that they are able to traverse the BBB and release their payload into the brain parenchyma [113]. Similarly, gemcitabine following incorporation into PBCA and coated with polysorbate 80 (Gem-PBCA + PS80) offered greater benefit in survival in a brain tumor model in rats compared to those treated with free gemcitabine [114]. Moreover PLGA NPs have been shown to facilitate their transfer across the BBB into the brain following intravenous administration in rats after conjugation with the sequence 12–32 (g21) of leptin [115]. These modified nanoparticles could be utilized as efficient carrier systems for delivery to brain tumors.

4.2. Chemical BBB disruption

4.2.1. Hyperosmolar BBB disruption

The strategies for chemically and noninvasively disrupting the BBB involve the co-administration of substances that are capable of transiently opening the BBB. They include the classical usage of high concentrations of osmotic agents, bradykinin analogues, and efflux pump inhibitors along with the recent combination of these options with polymeric and liposomal particles to result in a novel dual treatment strategy. A potential BBB modulating drug, the A2 agonist, regadenoson, has recently been shown to increase intracranial concentration of temozolomide in an animal model when both compounds were delivered systemically [73].

Hyperosmolar disruption of the BBB leads to the osmotic efflux of water from endothelial cells and their subsequent shrinkage and tight-junction dysfunction [116]. Different substances have been used as osmotic disruptors of the BBB, with mannitol being the most commonly used agent for this purpose [117–119]. First studies have suggested that this method can increase the concentration of various chemotherapeutic agents in the brain up to 90-fold [120]. Despite these initially encouraging results from a preliminary clinical study conducted in patients affected from lymphoma and treated with mannitol and cyclophosphamide [121], further studies have shown subsequent ineffective BBB disruption of the circumventricular organs [122] and non-selective disruption of the BBB surrounding tumors [104]. The non-selective nature of this treatment has thus raised concerns regarding its toxicity and efficacy throughout the CNS [123,124].

The potential of bradykinin analogs for enhancing BBB drug penetration is well known; however the mechanisms involved are under investigation [125,126]. Specifically, multiple mechanisms seem to contribute to the effect of bradykinin analogs on BBB permeability such as the reorganization and remodeling of transmembrane proteins of the tight junction which occurs after the stimulation of the B2 receptor, the upregulation of caveolin-1 and caveolin-2 at the BBB [127] which increases endothelial cell permeability, and the (K_{ATP}) channels which mediate the increase in permeability of brain tumor microvessels [128]. Bradykinin B2 receptor activation by Lobradimil (RMP-7) (Cereport) (Alkermes, Inc., Cambridge, MA, USA) was the first pharmacological example of treatment to show transient modification of the BBB in a receptor-mediated manner [129]. Preclinical and clinical trials have been conducted using RMP-7 in combination with carboplatin for the treatment of high grade glomas [130–132]; however the Phase II and III trials were halted due to low efficacy [133,134]. Another Phase II trial was conducted to investigate the effect in childhood high grade glioma and brainstem glioma, but also without effective results [135]. The lack of effectiveness in clinical trials has been attributed in part to the dose-limiting side effect of hypotension and to the differences between existing animal models and human patients [136]. The main drawback for the bradykinin analogs is that the effect of the receptors is exceedingly transient [127]. Additionally, the non-uniform distribution of their receptors in the brain ultimately resulted in insufficient intracranial and intratumoral distribution of the antitumor compounds [136].

Clinical interest in these BBB-modulating molecules, however, resumed after recent studies successfully combined them with nanoparticles. It has been shown that RMP-7 can facilitate the penetration of antiretroviral drugs through the BBB when grafted to the surface of methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) nanoparticles [137]. This bimodal treatment is particularly attractive because it combines the advantages of using a hyperosmotic agent and B2-agonists with drug-containing liposomes to reduce systemic exposure of non-targeted tissue to the drug as well as enhances drug uptake in the targeted tissue [138]. It has also been shown that hyperosmolar mannitol can increase the delivery of liposomally entrapped cAMP protein kinase to the brain [139]. Etoposide, angiotensin II [140], peptidase inhibitors, and [141] bradykinin enhance the uptake of drug-containing liposomes in the brain and are currently being explored in both the laboratory and in clinical trials for the therapy of different types of cancer [142,143].

4.2.2. Efflux pump-mediated mechanisms

Active efflux of anticancer drugs by P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated proteins (MRPs) contributes to tumors' mechanisms of resistance to chemotherapeutic and anti-cancer drugs. Thus, the co-administration of chemotherapeutic agents with specific inhibitors of efflux transporters has attracted much attention for disrupting the BBB in a noninvasive, specific, and rapid manner [144,145]. In preclinical models, P-gp inhibitors have been shown to improve CNS penetration of paclitaxel, docetaxel and imatinib [8,146]. The use of first-generation P-gp inhibitors, such as verapamil and cyclosporine A, resulted in low binding affinities, unacceptable toxicity, and the inhibition of drug-metabolizing cytochrome P450 3 A (CYP3A) enzymes. These findings rapidly led to the development of second-generation P-gp inhibitors, including the cyclosporine A analog, valspodar, which possessed stronger P-gp inhibition and lower toxic effects. Third generation modulators and inhibitors have included elacridar, zosuquidar, and tariquidar. These third generation inhibitors did not inhibit CYP3A and have demonstrated an improved side effects profile [147,148]. Among these inhibitors, the most promising results are with tariquidar, which binds P-gp noncompetitively at nanomolar concentrations [149] and has been shown to sufficiently inhibit P-gp at the BBB in vivo in animal models of brain tumor.

Concerns regarding the extent of enhanced clinical efficacy and the risks of adverse effects due to increased penetration of potentially toxic substances have only increased the search for effective and tolerable pump inhibitors that could revive agents otherwise rendered ineffective by efflux-mediated resistance. Pump inhibitors have been investigated in combination with nanoparticles, and in particular with paclitaxel-delivering nanoparticles. It has been shown that the usage of verapamil, one of the second-generation P-gp inhibitors, co-delivered in combination with either vincristine from PLGA nanoparticles or with paclitaxel in bi-functional micelles, restored vincristine and paclitaxel toxicity in multidrug resistant tumor cells [16,150]. Other studies using dual agent nanoparticles encapsulating the combination of paclitaxel and tariquidar have shown significantly higher antitumor effect whereas the nanoparticles loaded with paclitaxel alone were ineffective in a mouse model of drug resistant tumor [151]. Similar results have been achieved with the co-delivery of tariquidar/paclitaxel-loaded long-circulating liposomes [152] and elacridar-/paclitaxel-loaded long-circulating PEG-PE micelles using in vitro studies [153].

It has been shown that various efflux pump inhibitors can act together in the BBB. Accordingly, new inhibitors have been designed and synthesized to act against more than one efflux pump simultaneously. These dual inhibitors can inhibit P-gp and MRP1 (CBT-1) or P-gp and BCRP (nilotinib and sunitinib) [154]. Although the efficacy of these new dual inhibitors has not yet been fully elucidated, JAI-5 (P-gp and BCRP inhibitor) has been shown to delay the growth of tumor in a malignant glioma model in mice [155].

4.2.3. BBB modulating molecules

An important component of the BBB is the adherent junction, which is primarily composed of cadherin proteins. The binding of cadherin proteins to adjacent brain microvessel endothelial cells forms a homolytic dimer within the cell junction that limits the paracellular passage of solutes with a diameter greater than 11 Å, or approximately 500 Da [156,157]. The cadherin protein has an extracellular (EC) domain which consists of five tandem repeated units (EC-1 to EC-5) and the highly conserved region of His–Ala–Val (HAV) is involved in the formation of this dimer. Synthetic peptides based on the HAV region sequence have been studied with promising results. HAV peptides showed enhanced brain delivery of ^{14}C-mannitol and ^{3}H-daunomycin in an in

situ rat brain perfusion model [158], and have been shown to increase BBB permeability for both small and large molecular weight agents without any disruption in cerebral blood flow [159].

A number of other BBB modulating molecules are being developed. The observation that extracellular adenosine, produced by the catalytic action of CD73 (a 5′-ectonucleotidase) from adenosine monophosphate (AMP), promotes lymphocyte entry into the CNS in experimental autoimmune encephalomyelitis (EAE) [160] has encouraged attempts to modulate adenosine receptor (AR) signaling to improve the permeability of brain endothelial cells. Specifically, it has been shown that A_1 and A_{2A} AR activation facilitates the entry of intravenously administered macromolecules, including large dextrans and β-amyloid antibodies, into murine brains. Indeed, treatment with an FDA-approved selective A_{2A} agonist, Lexiscan, increased BBB permeability in murine models [161]. These changes in BBB permeability were dose-dependent and temporally discrete. This is a novel endogenous mechanism for controlling BBB permeability, which may represent a promising alternative to existing CNS drug delivery paradigms, especially considering that drugs like Lexiscan are already FDA-approved and in current clinical use [20]. Further studies are needed to determine exactly where AR-induced changes in BBB permeability occur in the brain microvasculature and whether these processes are local or global.

4.3. Physical BBB disruption (BBBD)

The term “physical disruption of the barrier” has been used to indicate the old and invasive method of bypassing a functional BBB using direct injections into the brain, either by direct injection into the ventricles or through carotid artery infusion. Recent efforts combine high-intensity focused ultrasound technologies, MRI-guided focused ultrasound, and nanostrategies to modulate the BBB in a more refined and non-invasive way. Physical BBB disruption consists of an armamentarium of technologies that seek to forcefully push therapeutic compounds and nanomaterials past the BBB by applying compressive sound waves, mechanical forces and thermo-ablative energy to trigger the action of anti-glioma agents in a highly site-specific manner.

4.3.1. Focused ultrasound

Focused ultrasound (FUS) has been investigated since the 1940's as a potential alternative to surgical resection and radiosurgery [162,163]. The feasibility and popularity of FUS over the past 10 years have firmly established the reputation of this imaging technique as a non-invasive and readily repeatable therapeutic strategy to selectively disrupt the BBB [164,165]. FUS concentrates acoustic energy at a focal point in order to induce shear stress on the targeted cells and activate signaling pathways, which in turn leads to selective disruption of the BBB [166]. The effects of FUS can be enhanced by combining ultrasound exposures (“sonications”) with preformed microbubbles that act as ultrasound imaging contrast agents [167]. The microbubbles consist of semi-rigid lipid or albumin shells that encapsulate a gas (typically a perfluorocarbon), range in size from 1 to 10 μm, and are constrained to the vasculature [167]. These microbubbles (MB) concentrate the ultrasound effects to the microvasculature, greatly reducing the FUS exposure levels needed to produce bioeffects. This combination, also known as MB-facilitated FUS, consists of circulating MBs that interact closely with low-intensity FUS and result in transient disassembly of tight junctions and enhanced permeability of the BBB [168–170]. Liu et al. have shown that MB-facilitated FUS temporarily disrupted the BBB transcranially and enhanced the penetration of BCNU up of 202% intratumorally in an orthotopic glioma model in rats [171]. This MB-FUS-system has been applied to different therapeutic molecules, including doxorubicin [172], temozolomide [173], methotrexate [174], siRNA [175], and stem cells [83]. Recent preclinical studies have confirmed that MB-enhanced FUS can successfully induce local BBB disruption with minimal side effects [176,177], as well as the ability to utilize real-time monitoring via MRI [178,179]. MRI-guided FUS with intravascular MBs has improved the systemic administration of different nanoparticle platforms by delivering genes, peptides and drugs selectively to the tumor site [180].

Densely poly(ethylene-*co*-glycol) (PEG)-coated brain-penetrating nanoparticles (BPNs) can be delivered selectively in cerebral regions where the BBB is disrupted by FUS and MBs [181]. The combination of drug-delivering nanoparticles with MB-facilitated FUS is becoming an attractive option for brain tumor-targeting therapy as it combines the advantages of a focused and effective disruption of the BBB with the advantages of using nanoparticles, which can be further modified to increase tumor cell specificity and diffusion in tumor. A study by Diaz et al. has shown that another class of nanoparticles, gold nanoparticles, can safely be introduced into the tumor periphery of a murine brain tumor model using MRI-guided FUS [182]. Non-PEGylated and highly PEGylated polymers with a polyethylenimine (PEI) core polymer were recently shown not only to cross the BBB but also to transfect the brain using MRI-guided FUS and MBs in a rodent model [183]. This study, in particular, represents the first evidence of brain transfection via the delivery of reporter gene-carrying nanoparticles across the BBB with FUS. This approach may represent a new method for effective brain tumor gene therapy [183,184]. Interestingly, FUS can improve tumor localization of molecules and nanoparticles not only following systemic administration but also following intranasal administration. In a mouse preclinical model, it has been shown that FUS enhances the intracranial concentration of intranasal administrated fluorescently-labeled dextran compared to that achieved by intranasal administration alone [185,186].

4.3.2. High-intensity focused ultrasound

The first attempts to evaluate the physical phenomenon of high-intensity focused ultrasound (HIFU) for clinical use in neurosurgery were conducted in the 1950's [187]. A Phase I/II study to treat brain tumors with image-controlled ablative HIFU was conducted in Israel in 2002 [188]. Beyond thermal ablation, HIFU has notably been shown to produce safe, nondestructive, and transient focal BBB disruption to facilitate drug delivery [170,189] and is being evaluated as a tool to induce hyperthermia to enhance the therapeutic effect of radiotherapy and chemotherapy [190]. HIFU has also been used noninvasively to enhance the local delivery of various macromolecules into different tissue types by decreasing the average energy intensities by using shorter pulses and shorter duty cycles [188,191]. The ability of ultrasound to disrupt the BBB using focused acoustic energy can also induce reversible BBB disruption without apparent acute tissue damage at the target site. This is therefore a promising method for brain tumor-targeting delivery strategies for drugs, antibodies, and genes [187,192,193]. Recently, HIFU has been used effectively to improve nanoparticle diffusion in the tumor environment by enhancing the extravasation of drug-loaded nanoparticles. Nanoparticles facilitate drug accumulation in tumors due to the EPR effect [191,194], but are severely limited in their convection ability due to the increased interstitial fluid pressure. The extravasation of convection-dependent agents, including nanoparticles, can be overcome by HIFU, which is able to increase the permeability of the vascular endothelial cells and allow the nanoparticles to escape the vascular space into the interstitial space of the tumor thereby resulting in improved distribution of the chemotherapeutic agent. MRI-HIFU also holds great promise for the application of hyperthermia in a non-invasive, localized and controlled manner. The integration of these systems with nanotechnologies has led to the development of a new strategy for local chemotherapeutic drug delivery based on temperature-sensitive liposomes (TSL). Here, chemotherapeutic agents are encapsulated into TSLs so that the drug can be selectively released at elevated temperatures when passing through a locally heated tumor. The concept of hyperthermia-triggered drug delivery using TSLs, as proposed by Yatvin and Weinstein [195], has been evaluated in preclinical models with various heat sources, such as needle-based radiofrequency (RF), water baths, light sources, and catheters [196–199]. Recently, multiple

preclinical studies have been published showing HIFU-induced drug delivery in mice, rats and rabbits [172,174,200,201]. The challenge of establishing and maintaining hyperthermia, as well as of monitoring the temperature non-invasively, strongly hampered the clinical translation of temperature-triggered drug delivery. The concept of temperature-triggered drug delivery has been extended to MR image-guided drug delivery by the co-encapsulation of a paramagnetic MRI contrast agent in the lumen of TSLs [202]; subsequent studies have been performed using MRI-HIFU in combination with paramagnetic TSLs using MR image-guidance [203]. Thirty years after the concept of local temperature-induced drug delivery was proposed, all technological parameters are in place for clinical translation. Importantly, the MRI-HIFU platform remains a minimally invasive approach for intracranially triggered drug delivery following systemic administration.

5. Conclusion

Over the past three decades, nanobiotechnological drug delivery methods have revolutionized traditional brain tumor-targeted therapy. Interstitial chemotherapy has paved the way for the development of new nano- and bio-medical platforms that optimize the delivery of therapeutics to the brain. Intracranial delivery, from both local and systemic routes, has witnessed great strides in preclinical studies, both in vitro and in animal models of CNS disease. Multiple options are poised to be proven effective in Phase I/II trials in the clinical setting. Following the success of BBB permeability modulation, classical diagnostic and therapeutic imaging techniques such as HIFU, US and MRI are finding novel applications to facilitate the penetration of the BBB and the selective and effective delivery of drugs or genes into the sites of malignancy. The current integration of nano- and bio-technologies and theranostic and imaging techniques is set to lead a paradigmatic shift in the armamentarium for tumor-targeted drug delivery and offer new options for the treatment of brain tumor.

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