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Harnessing nanomedicine for therapeutic intervention in glioblastoma

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\textbf{ABSTRACT}

\textbf{Introduction:} Glioblastoma is a type of brain cancer arises from glial cells. Glioblastoma multiforme (GBM), a subtype of glioblastoma, is the most common and most aggressive primary brain tumor. Currently, GBM therapy includes surgery and post-operative high-doses of radiation and chemotherapy. This therapeutic strategy has a limited contribution in extending the survival rate of GBM patients.

\textbf{Areas covered:} Herein, we focus on harnessing nanoscale drug delivery strategies to treat brain malignancies. Specifically, we briefly discuss the challenges facing GBM therapy such as restricted passage across the blood-brain barrier (BBB) and low enhanced permeability and retention effect. Next, we describe different pathways to address these challenges. Finally, we discuss the field of nanomedicine, which emerged as a promising platform for drug delivery to brain malignancies.

\textbf{Expert opinion:} Countless strategies have been applied in preclinical and clinical settings to treat GBM. Among them is the use of different types of nanoparticles (NPs) and viruses with different approaches to cross or bypass the BBB. We suggest here a paradigm shift in thinking about crossing the BBB and tumor penetration as fundamental issues that need to be address in order to improve the therapeutic outcome in GBM.

\textbf{1. Introduction}

Glioma is a general term to describe any tumor arises from glial cells that function as the supportive tissue of the brain and is responsible for the health of nerve cells within the brain. Gliomas are accounting for almost 80% of all malignant brain tumors and considered as the most lethal one. Gliomas are classified by the origin of the cells they arose from and the extent of the infiltration into the brain tissue. The three subtypes of cells gliomas arise from are astrocytes, oligodendrocytes, and ependymal cells, which produce astrocytoma, oligodendroglioma, and ependymoma, respectively. Tumors that display a mixture of these cells are called mixed gliomas. There is also an optic nerve glioma and brain stem glioma that are named for their locations rather than the tissue type from which they originated [1]. The different types of gliomas are graded on a scale from I to III based on the abnormality of the cells, except of astrocytoma, which presents also grade IV and referred as glioblastoma multiforme (GBM) [2]. The malignancy grading can be divided into two subgroups: low-grade glioma, which contains grades I and II and high-grade glioma, which contains grades III and IV gliomas [1,2]. Astrocytomas are the most common type of glioma, which accounts for more than 75% of all gliomas [3]. There are two types of astrocytoma grade IV – primary, or de novo, and secondary. Primary tumors are very aggressive and are the most common form of astrocytoma grade IV. The secondary tumors are those, which originated as a lower grade tumor and progressed into a grade IV tumor [1]. GBM is considered the most aggressive primary central nervous system (CNS) malignancy because of its increased cellular proliferation rate, significant high invasive ability, angiogenesis, resistance to apoptosis, and genomic aberrations compared with grades II and III astrocytomas [4].

The incidence of all of primary brain and CNS tumors is estimated at 18.71 per 100,000 individuals per year, whereas GBM has an incident rate of 3.19 per 100,000 individuals and a median survival of 15 months [5]. The common neurological symptoms presented by patients with gliomas are headaches, seizures, focal neurologic deficits, memory loss, personality changes, vomiting, and visual changes [3,6].

GBM is considered a complex malignancy with multiple gene mutations, aberrations and overexpression. Low-grade gliomas carry a mutation in the isocitrate dehydrogenase 1 or 2 (IDH1/IDH2) gene, and it was recently proposed that primary versus secondary glioblastoma definitions can be based on the IDH1/IDH2 mutation status of the tumor [7]. High-grade gliomas are characterized by significant overexpression of many other genes (e.g. EGFR, CDK4, MDM2, etc.) that contribute for its high proliferation rate, invasion, angiogenesis, and necrosis [4,8]. Currently, the treatment for GBM is complex and consists of surgical resection followed by radiation therapy (RT) with concurrent temozolomide (TMZ) chemotherapy [9]. This therapeutic strategy has not changed for over a decade, since TMZ was approved in 2005 [10] and has a very limited contribution in extending GBM patients' life expectancy. Moreover, some groups have reported survival benefits when...
GBM is considered the most aggressive primary CNS malignancy with very low survival rate. Currently, the therapeutic modalities consist of surgical resection followed by radiation therapy (RT) with concurrent temozolomide (TMZ) chemotherapy with a limited contribution in extending GBM patients' life expectancy. Many hurdles in drug delivery to the brain prevent the development of novel and more potent drugs to overcome this malignancy. Harnessing nanomedicine for drug delivery can overcome many of the hurdles due to its ability to be tailormade to achieve many goals such as bypassing the tight restriction to the brain. Bypassing the restriction of the BBB can be achieved by different drug delivery pathways such as intracranial injections or intranasal administration or by modifying the NPs to cross through the BBB by different pathways. Nanomedicine has the potential of introducing real breakthrough in GBM care. The extent of resection was used as a prognostic factor [2,11]. Additionally, a multicenter phase III trial comparing fluorescence guided microsurgery with conventional microsurgery of glioblastomas showed a survival benefit in patients who underwent complete tumor resection according to the assessment of residual contrast enhancement on postoperative magnetic resonance imaging (MRI) [12,13]. A greater awareness of the effect of maximal resection of brain lesions over the last decade has led to increased utilization of MRI as an intraoperative imaging technique for guidance in neurosurgical procedures [14,15].

However, despite advances in imaging techniques and multimodal treatment options, the overall prognosis of patients with GBM remains grim. The median duration of patient survival is estimated to be between 12 and 18 months with maximal treatment, and those without any intervention succumb soon after diagnosis. Unfortunately, only 2–5% of the patients survive for more than 3 years and are referred to as long-term survivors. Favorable clinical factors, in particular young age, good initial performance score, as well as hypermethylation of the O6-methylguanine-DNA-methyltransferase promoter were associated in long-term survival in GBM patients [16,17].

GBM has an unfavorable prognosis mainly due to its high propensity for tumor recurrence. It has been suggested that GBM recurrence is inevitable after a median survival time of 32–36 weeks. Studies have shown that GBM recurrence most often occurs in the form of a local continuous growth within 2–3 cm from the border of the original lesion. More than 90% of patients with glioma showed recurrence at the original tumor location and that multiple lesions developed in 5% after treatment. The role of re-resection by itself remains unclear and most patients receive postoperative chemotherapy all failed in treating patients with high-grade GBM. Novel therapeutic strategies in treating GBM patients are therefore of great need. Patients undergo intense treatments ending with poor outcomes.

Nanoparticles (NPs) that can carry drugs and often are called nanomedicine creates a unique opportunity to study and optimize the current treatment for brain tumors, hence, has the potential of introducing real breakthrough in GBM care.

2. Hurdles in brain delivery strategies

The brain is one of the most protected organ within the body as it provides control over the entire actions of the organism. As it does so, it has many protective shields in the form of a skull, meninges, cerebrospinal fluid, and the blood–brain barrier (BBB) [19]. All of these not only help to protect the brain from injuries and diseases, but also challenge the therapy in such cases by decreasing the accessibility to the brain.

2.1. BBB

The main obstacle for drugs to penetrate the brain is the BBB. The BBB is a highly selective barrier, which line the blood vessels in the brain and spinal cord [20]. Its main purpose is to act as a physical barrier in order to protect the brain and the spinal cord from passage of drugs, neurotoxins, invading organisms and to regulate the movement of essential nutrients between the systemic circulation and the brain tissue [21]. The BBB is formed by specialized brain endothelial cells called cerebral endothelial cells (CECs) along with other perivascular cells such as pericytes, astrocytes and perivascular macrophages [20]. These CECs are bound by tight junctions in order to limit the movement mostly of metabolites across the cells in a transcellular transport but also between adjacent cells in a paracellular transport as in most endothelial cells [22]. The BBB is essential for proper brain functions for the selective supply of oxygen and nutrients such as glucose [23]. Each cell comprised the BBB has its unique function in maintaining the homeostasis of the brain tissue. The astrocytes, which cover the basal lamina of the brain capillaries provide the cellular connection to the neurons [24]. The pericytes contribute to the integrity of the BBB and control the blood flow within the blood vessels [25]. The perivascular macrophages play an immunoregulatory role and prevent the entrance of agents to the CNS from the systemic circulation [26]. This complex and tight structure is the first interface any large molecule meets in the passage to the CNS. Except for some very small or gaseous molecules such as water or carbon dioxide, which can passively diffuse through the lipid membrane of the endothelial cells, other metabolites use specific transport system composed of receptors and transporters to pass through the BBB [27] (Figure 1). This specific transport system regulates the transcellular traffic by either permitting the entrance of necessary nutrients or effluxing potentially harmful compounds [28]. Different metabolites, such as hydrophilic molecules, proteins, glucose, lipid-soluble agents can be transferred through the BBB by either passive or active transport. The passive passage can be for either water-soluble agents through the tight junction (Figure 1(a)) or lipid soluble agents through the endothelium (Figure 1(b)). The active passage involves either transporter or receptors in a transporter/
receptor mediated transcytosis or by adsorptive mediated transcytosis [29]. This complexity severely restricts the entry of drugs to the CNS and thus any strategies for drug delivery should take these transport systems into account. Since there are many kinds of transport systems that provide the brain with its necessary nutrients, focusing on at least one will be necessary in devising the delivery system of a desired drug. Transporter-mediated transcytosis is a substrate selective so the drug must be capable to mimic the endogenous substrate in order to be taken up and transported into the brain [30]. One such target can be the glucose transporter (GLUT), which transports glucose. It has been shown that drugs incorporated with mannose were able to cross the BBB via the GLUT1 in a mouse brain [31] (Figure 1(c)). The receptor-mediated transcytosis method shows characteristics of high specificity, selectivity, and affinity rather than the transporter-mediated transcytosis pathway because it decreases the need for the drug to mimic the endogenous ligand [32]. There are several receptors expressed on the endothelium of the brain that can be used in devising delivery strategies. Examples can include the transferrin receptor (TfR) [33], low-density lipoprotein receptor (LDLR) [34], insulin receptor [35], and many other receptors. One of the most widely characterized receptor-mediated transcytosis strategies is the TfR, which is highly expressed on endothelial cells of the BBB. Drugs conjugated with transferrin or monoclonal antibody against TfR has been extensively studied and will be discussed in more detail in this review (Figure 1(d)). Finally, an adsorptive-mediated transcytosis mechanism provides a delivery strategy across the BBB by cationic proteins or cell penetrating peptides. These interactions are based on electrostatic interactions between the positively charged moieties on the surface of the drug to the negatively charged membrane of the endothelial cells [36,37] (Figure 1(e)).

2.2. Blood–brain tumor barrier

Pathological conditions (e.g. brain cancer, multiple sclerosis, dementia, and more) can alter the structure, function and organization of the BBB [20,25,38]. In the case of brain malignancies, a blood–brain tumor barrier (BBTB) can be formed with the deterioration of the brain tumor. In low-grade gliomas, the growth and proliferation of the tumor depends on the existent vascular system; however, as the glioma advances toward a high-grade glioma, tumor cells begin to invade to surrounding healthy brain tissue and the normal BBB becomes damaged. At this point, the BBTB will be formed by CECs and replace the BBB [39]. Upon formation of the BBTB, it becomes the main obstacle for nanoscale drug delivery systems to penetrate into the brain tissue by limiting the delivery of most hydrophilic molecules to the tumor tissue [40]. High-grade gliomas demand high metabolic rate, therefore, trigger an increase in the expression of vascular endothelial growth factor and angiogenesis to hypoxic areas, leading to the formation of abnormal blood vessels and dysfunctional BBTB [41]. Drug therapy strategies proposed for crossing the BBTB take into consideration these pathological features and are being targeted to the highly expressed EGFR or to cell adhesion molecules and integrins. With further progression of the tumor, the BBTB becomes also disrupted and impaired by the formation of gaps in the endothelial cells contributing to is ‘leaky’ feature as was shown by MRI [42]. This physiological phenomenon named enhanced permeability and retention (EPR) will be discussed below.

2.3. EPR effect in brain tumors

As the tumor grows and develops, there is a stimulation for increased production of blood vessels to the tumor, causing an increase of the EPR effect [43–45]. This property may aid macromolecules and NPs of certain sizes accumulating in tumor tissues [46–49]. In the brain tissue, the EPR effect appears as the tumor develops although it is significantly less pronounced in the brain microenvironment than in other types of tumors [50–52]. The weak EPR effect decreases the passage of therapeutics from blood vessels to the brain tissue, thereby resulting in low efficiency of drug delivery into the brain tumor.
2.4. Diffusion of drugs and delivery systems within the brain

High-grade gliomas as opposed to low-grade gliomas are characterized by high infiltrative ability, thus, are able to extend out of the main tumor mass [53]. Therefore, the potential therapeutics should not only be able to pass through the BBB/BBTB but also should be able to diffuse within the brain tissue for an effective treatment. Currently, surgical resection is usually the initial step in treatment but the infiltrative nature of the tumor cells complicates the surgical resection, as it is impossible for the surgeon to visualize all tumor cells, and remove them without extensive damage to the surrounding brain tissue [54]. As a result of this partially removal of tumor cells, the majority of recurrences are adjacent to the initial tumor site [55]. For a complete removal of all tumor cells, in the hope for a remission, it is imperative that the drug or drug carrier will be able to effectively diffuse through the brain tissue. Several methods have been employed in order to enhance the interstitial movement of therapeutics throughout the tumor. One important feature of the therapeutic particles is the optimal size for movement within the brain. It has been suggested that the width of the drug carrier should be approximately 30–70 nm in diameter [56]. Another important feature is the composition and the surface properties of the carriers, which can influence the diffusion through the brain, and even overcome the size hurdle. It has been shown that a dense layer of polyethylene glycol coating improves the penetration of NPs with mean diameter of 114 nm, within the brain tissue [57].

2.5. Nonspecific delivery to healthy cells

The challenges discussed thus far are particularly to brain tumors, however, as with other cancers the specific targeting to the malignant cells is an important hurdle that must be addressed. Systemic or localized treatment must be designed for minimal damage to healthy tissues: either the brain or other organs. To this end, the use of NPs can be highly advantageous due to their ability to be modified and tailored made to include one or several layers of delivery specificities. The addition of targeting moieties on the surface of the NPs can enable a specific recognition of malignant cells compared to healthy cells. One such targeting moiety is hyaluronan (HA), which is a ligand for CD44, a cell surface glycoprotein, that was previously shown to be overexpressed on many types of malignant cells [58–60] in general and glioma cells [61] in particular.

3. Bypassing the BBB: different delivery pathways

The presence of the BBB that segregates the brain from the circulatory blood system not only protects the brain from invading organisms and neurotoxins, but also prevents the entrance of therapeutics under pathological conditions. Several strategies have been employed to either deliver drugs across the BBB or bypass it. The ideal method for transporting drugs to the brain should either cross it in a controlled manner without causing any damage to it or bypass it in an effective manner that will lead to specific binding to the malignant cells. Among the various approaches, nanobiotechnology-based delivery methods provide a major opportunity for achieving this goal.

3.1. Intracranial injections

Intracranial drug delivery approaches attempt to bypass the BBB by a direct delivery into the tumor mass. There are several approaches to intracranial delivery: intracerebral implantation, intracerebroventricular infusion, and convection-enhanced diffusion (CED). One method for the intracerebral implantation approach is based on polymers that can release drugs in a time-controlled manner at the site of tumor resection [62–64]. The advantage of this approach is that the localized drug delivery device provides high drug concentrations directly to the tumor site while avoiding systemic toxicity and protecting the drug from degradation and clearance by the immune system until its release [65–68]. Brem et al. showed that local delivery of TMZ, the primary chemotherapy used for the treatment of GBM, has improved the survival of tumor bearing animals compared with systemic administration of TMZ. Additionally, concurrent treatment of intracranial TMZ with RT showed improved survival compared to those with intracranial TMZ alone or oral TMZ with radiation [65]. Cohen et al. suggested another local approach based on direct injections of HA coated NPs encapsulated with RNA interference to the tumor mass. As a result, a dramatically prolongation of tumor-bearing mice survival was shown, beyond any published reports in the same model [61] (Figure 2(a) and Table 1).
Table 1. NPs for the treatment of GBM.

<table>
<thead>
<tr>
<th>Carrier type</th>
<th>Drug in NPs</th>
<th>Targeting approach</th>
<th>Delivery pathway</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Microspheres</td>
<td>5-FU</td>
<td>Direct</td>
<td>Intracranial</td>
<td>[62]</td>
</tr>
<tr>
<td>PNPs</td>
<td>TMZ</td>
<td>Direct</td>
<td>Intracranial</td>
<td>[63,65]</td>
</tr>
<tr>
<td>PNPs</td>
<td>BCNU</td>
<td>Direct</td>
<td>Intracranial</td>
<td>[64,66]</td>
</tr>
<tr>
<td>LNPs</td>
<td>siPLK1</td>
<td>Direct</td>
<td>Intracranial</td>
<td>[61]</td>
</tr>
<tr>
<td>PNPs</td>
<td>Carboplatin</td>
<td>Local</td>
<td>Intranasal</td>
<td>[70]</td>
</tr>
<tr>
<td>Micelles</td>
<td>siRaf-1 and CPT</td>
<td>Local</td>
<td>Intranasal</td>
<td>[71]</td>
</tr>
<tr>
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<td>Paclitaxel</td>
<td>Systemic – active</td>
<td>IV</td>
<td>[31,72]</td>
</tr>
<tr>
<td>LNPs</td>
<td>DOX</td>
<td>Systemic – active</td>
<td>IV</td>
<td>[50]</td>
</tr>
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<td>Daunorubicin</td>
<td>Systemic – active</td>
<td>IV</td>
<td>[73]</td>
</tr>
<tr>
<td>PNPs</td>
<td>DOX and PTX</td>
<td>Systemic – active</td>
<td>IV</td>
<td>[74]</td>
</tr>
<tr>
<td>LNPs</td>
<td>DOX</td>
<td>Systemic – passive</td>
<td>IV</td>
<td>[75–79]</td>
</tr>
</tbody>
</table>

*aActive transport through the transporter mediated transcytosis.
*bActive transport through the receptor mediated transcytosis.

PNPs: nanoparticles; PNPs: polymeric-based NPs; LNPs: lipid-based NPs; TMZ: temozolomide; BCNU: biodegradable carmustine; IV: intravenous; DOX: Doxorubicin; PTX: Paclitaxel.

3.2. Intranasal administration

Intranasal administration of targeted therapeutics to brain tumors has many benefits, first and foremost is the ability to bypass the BBB and to provide an alternative to invasive methods of drug administration to the CNS [80,81]. This noninvasive method allows a drug delivery pathway that reduces the systemic exposure and side effects. Furthermore, this method of delivery is simple, rapid and therapeutics can reach the brain within minutes from administration [81]. The neural connection between the nasal mucosa and the brain provides a unique pathway for noninvasive delivery of therapeutic agents to the CNS. All agents administered intranasally reach the brain via the olfactory and/or the trigeminal neural pathways. Both of these nerves innervate to the nasal cavity, allowing a direct connection to the CNS [81]. At first, this delivery route was mainly researched for the delivery of proteins for neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, epilepsy, and more [69]. The neurotrophins: nerve growth factor [82,83] and insulin-like growth factor 1 [84], the cytokine interferon beta-1β [85], and others were successfully delivered to the CNS by intranasal delivery both by the olfactory and by the trigeminal nerve pathways. Recently, NPs’ delivery by intranasal approach to treat brain tumors has been developed in order to find novel strategies for therapy of brain tumors [70,86]. Kanazawa et al. showed that intranasal delivery of NPs in the form of micelles co-loaded with a drug and siRNA can reach the tumor and prolong the life of rats with malignant glioma [71] (Figure 2b and Table 1).

3.3. Intravenous administration

Systemic administration encounters all the barriers previously discussed above. The use of NPs has emerged as a potential strategy for diagnosis and treatment of tumors in general and GBM in particular due to the ease of surface modification that can be employed in NPs in order to address the different barriers [45,87]. When referring to the BBB or BBTB, NPs can be coated with targeting ligands that will enable the NPs to cross safely through the BBB/BBTB. Most NPs are targeted to a specific endogenous receptor or transporter in order to achieve an improved passage through the barrier and that the drug will be able to reach the brain in a therapeutically relevant dose. An interesting strategy to temporarily disrupt the BBB and allow the NPs to enter is the use of focused ultrasound (FUS) [88]. It was shown that FUS, when combined with circulating microbubbles, can temporarily permeabilize the BBB without tissue damage. Furthermore, when liposomal doxorubicin were administrated together with FUS, a significant increase in the survival of rat glioma was observed compared to all other controls [89]. This technique can enhance the delivery of NPs by bypassing the BBB and BBTB while causing temporarily gaps within their structure (Figure 2c and Table 1).

4. NPs as a novel delivery strategy for gliomas treatment

4.1. Types of NPs used in drug delivery

Over the last few decades, the use of NPs has gained huge research focus and emerged as a highly potential drug delivery modality, targeting specific drugs to sites of interest [45]. The key advantage of utilizing NPs as delivery platforms is the ability to tailor-made them to achieve both controlled drug release and tissue specificity. Therefore, NPs can be used for both diagnosis and treatment for not only malignancies but other types of diseases [90,91]. NPs can carry a range of different drugs including chemotherapy (e.g. doxorubicin, paclitaxel, TMZ, and more), nucleic acids (siRNAs, miRNAs, mRNA, plasmid DNA, etc), or proteins (toxins, antibodies, and enzymes). NPs can protect the drug from degradation, increase the plasma concentration half-life, reduce toxic effects, and release the content of the NPs in a controlled release manner. The size of the NPs should not be over 200 nm in diameter and should not produce an immune response. Generally, NPs below 100 nm in size are cleared slower and predicted to accumulate to a greater extent in tumors [92]. There are several subgroups of NPs, made from different materials currently used for therapeutic or diagnostic modalities.

4.1.1. Lipid-based NPs

Lipid-based NPs (LNPs) are the most veteran delivery vesicles, composed of lipids similar to those of biological membranes (e.g. phospholipids and cholesterol) and possess an aqueous core. LNPs can come in different forms such as liposomes, solid LNPs, nanoemulsions, and more (Figure 3a,d)). The most common and highly used form of LNPs is liposomes. Liposomes can vary in size and in number of lipid bilayers surrounding the core and can form small unilamellar vesicles, large unilamellar vesicles, or multilamellar liposomes [93]. The composition of the lipids can also vary between different liposomes and can form pH sensitive liposomes, cationic...
Different nanoparticles utilized for drug delivery. (a) LNPs conjugated to antibodies or to polymers to enhance blood-brain barrier penetration. (b) Biodegradable polymer nanospheres. (c) Biodegradable polymer nanocapsules. (d) Solid lipid particles. Adapted with permission from ref [69].

liposomes, immunoliposomes, or long-circulating liposomes that will affect greatly on the delivery mechanism. The aqueous core of the liposome can entrap water-soluble drugs while the lipid bilayer can entrap lipophilic drugs, thus enabling the delivery of both hydrophilic and hydrophobic drugs [94]. Currently, there are more than 10 approved liposomal drugs entrapping chemotherapeutic agents [45].

4.1.2. Polymeric NPs
Polymeric based NPs (PNPs) are solid particles composed of natural (e.g. gelatin, alginate, collagen, and chitosan) or synthetic polymers (e.g. polylactide-co-glycolide, and polyethyleneimine) (Figure 3(b,c)). These polymeric materials were proven as biodegradable, biocompatible, nontoxic, and non-immunogenic [95]. PNPs can entrap both lipophilic and hydrophilic drugs by either entrapment in the NP matrix in a solid form or in a solution if the PNP core is liquid. In addition, PNPs can covalently bind the therapeutic moiety to the particle surface [45]. Another form of PNPs is micelles, consist of amphiphilic polymers, which self-assemble in an aqueous environment into nanostructures composed of a hydrophilic shell and a hydrophobic core [96]. Hydrophobic drugs can be entrapped within the hydrophobic core, protecting it from degradation and rapid clearance in the blood, while the hydrophilic shell provides stability in the blood, thus enabling prolonged circulation time in the body [97].

4.1.3. Inorganic NPs
Inorganic NPs are a class of NPs that contain inorganic molecules such as iron oxide, gold, ceramic, silver based NPs, and more. This class of NPs can be utilized for drug delivery purposes but also emerges as highly potential method for imaging and diagnosis of brain tumors. Gold (Au) NPs are extremely small in size with a mean diameter of <15 nm, thus allowing their uptake through the ‘leaky’ brain tumor barrier. AuNPs have a dual role since they can be used for imaging by CT scans allowing the use of this method for diagnosis. In addition, radiation of AuNPs enhances the beneficial effect of radiation treatment alone, thus might impact the long-term survival [98]. Iron oxide NPs are already being used as MRI contrast agents [99] and are under investigation as drug delivery vehicles [100]. Quantum dots (QD) are emerging as a new class of NPs for in vivo imaging and therapeutics. QD have the ability to adsorb white light and reemit it within nanoseconds. They have broad excitation spectrum, narrow emission spectrum, good photo-stability, and long fluorescent lifetime and finally could be easily functionalized with targeting ligands for targeted delivery purposes [101,102].

4.2. NPs for glioma treatment
NPs can potentially cross the BBB or BBTB by either passive uptake through the inter-endothelial gaps of the ‘leaky’ BBB due to their small size or by targeted uptake using means of adsorptive-mediated transcytosis or receptor-mediated transcytosis using surface functionalized NPs. This also enables these surface-functionalyzed NPs to specifically target the malignant cells rather than the normal cells, thus allowing preferentially accumulation of the NPs at the brain tumor tissue. Another advantage of NPs is their ability to carry different types of anticancer agents or markers as previously described. NPs have been studied extensively for brain-targeted drug delivery either by localized manner or systemic delivery. Local delivery of therapeutic agents bypasses the limitation of the BBB compared to a systemic delivery approach. Initial studies focused on the implantation of drug-loaded biodegradable polymer wafers (Gliadel®), which are able to release drugs in a controlled manner over a prolonged period of time. Although the results showed improvement in patient survival [103], the drug released from the implants had limited ability to penetrate into the tumor mass [104]. Next, a convection-enhanced drug delivery (CED) approach was established. CED is based on delivering a continuous infusion of drugs through intracranial catheters, enabling distribution of high doses of drugs over large volumes to the brain. This delivery strategy can use both LNPs [105] and PNPs [106] as therapeutic drug carriers released from the catheters. Recently, it was shown that localized delivery of LNPs coated with the glycosaminoglycan HA, a natural ligand of the CD44 receptor that is highly expressed on GBM cells, can be used for local delivery. Cohen et al., encapsulated siRNA against Polo-like Kinase 1 in these HA-LNPs and demonstrated a robust in vivo gene silencing of GBM cells engrafted in the brain of nude mice. In addition, they showed a remarkable improvement in the survival of glioma bearing mice [61].
Systemic delivery of NPs to the brain is based on their potential to pass through the BBB by either passive or active targeting. Since there are many kinds of receptors expressed on the endothelial BBB, different studies attempted to exploit some of them to facilitate the transport of NPs. Among the most common receptors extensively studied are the GLUT [31,73,107,108], TFR [33,73,109–111], LDLR [74,112], and glutathione transporters [72,113,114]. It was also shown that dual targeting can improve the BBB passage by adding two targeting moieties: one that first targets the BBB and then targets specifically the glioma cells [31,73,74]. Another type of systemic delivery approach that can be used is oral administration route. Recently, Thiyagarajan et al. described an enteric-coated NPs incorporated with focal adhesion kinase inhibitor administered orally that showed decrease in tumor volume as compared to other controls in this study [115]. Although the active targeting to the BBB by systemic administration is a promising method of drug delivery to GBM, most of the FDA approved or undergoing clinical trials are the ones that are passively targeted [75–79].

5. Conclusions

Herein, we summarizes the biological nature of GBM tumors, the devastating outcome for patients, the difficulties modern medicine is facing in the treatment of this disease, and present novel therapeutic strategies for intervention in GBM tumors. Current therapy, which includes surgical resection, and chemotherapy with radiation does not provide a long-term solution for patients with GBM. There is a need for novel and beneficial treatment, which will prolong the survival rate of these patients while improving their quality of life. Harnessing nanomedicine for therapeutic intervention in GBM can provide an opportunity for this unmet need. The ability of nanomedicine to bypass many of the hurdles standing in the way of drug delivery to the brain provides new hope for treating GBM. The deeper understanding of the BBB and ways to transport drugs via different administration routes using targeted NPs may open new avenues for improving both the life expectancy and quality of life of patients with gliomas.

6. Expert opinion

GBM is an incurable disease with a median survival of 12–15 months. We are still far from changing the therapeutic modality of GBM with NPs, but we have learned that crossing the BBB or bypassing the BBB using different methods is doable. Several fundamental questions remain to be determined. Among these questions: can we utilized targeted NPs as delivery vehicles to GBM? What is the ability of NPs to cross the BBB and diffuse effectively in the brain’s parenchyma and penetrate into the tumor mass and/or into the metastasized tumors while delivering therapeutically relevant doses of the desired drugs and what are the key players among the various proteins that dictate the metastasis and drug resistance phenotype observed in GBM?

Other questions relate to what is the uniqueness of patients that survive more than the median time? Which genes are upregulated in these patients and what mutations they pose in their DNA? Answering these questions will provide new insights into the design of targeted NPs that can utilize these mechanisms and effectively deliver new drugs into the brain tumor.

We are entering the precision (personalized) medicine area where every patient counts [116,117] and the implications are that many of these GBM tumors are now being analyzed at the DNA and RNA levels in order to better understand the mutations, chromosomal alternations, and transcriptome and to fit the best treatment option(s) to the patient. In addition, the utilization of RNA drugs and combination of RNA drugs with novel immune oncology strategies may reprogram the tumor microenvironment and dramatically improve the therapeutic outcome of GBM patients.

It is likely that one of these strategies alone or in combination with other approaches might become therapeutically successful and will aid in establishing NPs as a novel therapeutic modality for GBM.

Declaration of interest

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Papers of special note have been highlighted as:
• of interest
•• of considerable interest

•• This manuscript summarizes all the genetic alterations in GBM based on patients’ samples.
This review summarizes the biology of the BBB and emphasizes it as the main obstacle in drug delivery to the brain.


This review summarizes different strategies to increase the delivery of therapeutics across the BBB and BBTB.


This review summarizes the potential of nanoscale drug delivery methods for cancer therapeutics.

This manuscript emphasizes the benefits of local delivery to the brain as a means of bypassing many hurdles in brain tumor therapy.


This review summarizes the intranasal delivery platform to the brain as a means to bypass the BBB.


This manuscript presents a novel method for temporally disruption of the BBB enabling the entrance of therapeutic NPs to the brain.


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