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Ultrasound-responsive nanoparticles for imaging and therapy of brain tumors

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ABSTRACT

Central nervous system (CNS) cancers, particularly glioblastoma (GBM), are associated with high mortality and disability rates. Despite aggressive surgical resection, radiotherapy, and chemotherapy, patient survival remains poor. The blood-brain barrier (BBB) significantly impedes therapeutic efficacy, making BBB penetration a critical focus of research. Focused ultrasound (FUS) combined with microbubbles (MBs) can transiently open the BBB through mechanisms such as cavitation, modulation of tight junction protein expression, and enhanced vesicular transport in endothelial cells. This review highlights precision delivery and personalized treatment strategies under ultrasound visualization, including precise control of ultrasound parameters and modulation of the immune microenvironment. We discuss the applications of ultrasound-responsive nanoparticles in brain tumor therapy, including enhanced radiotherapy, gene delivery, immunotherapy, and sonodynamic therapy (SDT), with a particular emphasis on piezoelectric catalytic immunotherapy. Finally, we provide insights into the clinical translation potential of ultrasound-responsive nanoparticles for personalized and precision treatment of brain tumors.

1. Introduction

Central nervous system (CNS) cancers are associated with high mortality and disability rates, with clinical manifestations varying based on histopathology and anatomical involvement [1]. Over the past three decades, the global burden of CNS cancers has increased [2,3], and the age-standardized incidence rate (ASIR) is projected to rise further over the next 25 years, particularly among females [4]. CNS cancers are the most common cancer type in children aged 0–14 years, with an average annual age-adjusted incidence rate (AAAIR) of 5.74 per 100,000 [4]. However, incidence and mortality rates in the 1–10 age group have significantly declined since 2019 [2]. Glioblastoma (GBM), the most common malignant CNS tumor, is typically treated with surgical resection followed by radiotherapy and chemotherapy. Although emerging therapies such as immunotherapy, chronotherapy, and oncolytic virotherapy are under development to improve outcomes and minimize adverse effects [5–8], GBM remains a challenging disease with a nearly universal fatality within two years of diagnosis, imposing significant economic and medical burdens on families and society [9–12].

The blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (CSF), and blood-tumor barrier (BTB) are major obstacles in brain tumor therapy [13]. The BBB prevents harmful endogenous and exogenous molecules from entering the brain, limiting drug delivery to target sites and posing a significant challenge for neurological disease treatment [14–16]. The CSF barrier restricts the passage of most macromolecules from the blood to the cerebrospinal fluid, hindering systemic drug delivery for brain tumors [17,18]. The BTB, characterized by high interstitial pressure due to leaky tumor vasculature, limits drug penetration from the bloodstream into the tumor [19]. However, the presence of 10–30 nm pores between endothelial cells forming the BBB makes nanomaterials promising for brain tumor therapy [16,20].

Nanomaterials, with their small size, large surface area, enhanced retention, and high permeability in tumor regions, have become valuable tools for tumor imaging and therapy [21]. Currently,

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contrast-enhanced magnetic resonance imaging (MRI) is the most common method for brain tumor diagnosis, with gold nanoprobes [22], superparamagnetic iron oxide (SPIO) [23], and gadolinium nanoparticles [24] clearly defining tumor boundaries. Although MRI offers high spatial resolution, it is associated with complex procedures, high costs, and gadolinium-induced nephrotoxicity [25]. Interestingly, ultrasound-triggered nanoparticles can open the BBB and deliver drugs to tumor tissues [26], and when loaded with sonosensitizers, they can enable sonodynamic therapy (SDT) [27,28]. Ultrasound, with its real-time, portable, non-invasive, and cost-effective advantages, shows significant promise in brain tumor therapy, particularly in overcoming BBB limitations, enhancing drug delivery efficiency, and enabling precision medicine [29,30].

This review systematically elucidates the mechanisms of ultrasound-responsive nanoparticle-induced BBB opening, including macroscopic cavitation effects and microscopic molecular mechanisms (e.g., modulation of tight junction protein expression and enhanced vesicular transport in endothelial cells). Based on bibliometric analysis, we discuss current research hotspots in brain tumor nanotheranostics. We focus on precision delivery and personalized treatment strategies under ultrasound visualization, including precise control of ultrasound parameters and modulation of the immune microenvironment. We also explore the applications of ultrasound-responsive nanoparticles in brain tumor therapy, including enhanced radiotherapy, gene delivery, immunotherapy, and SDT, with a particular emphasis on piezoelectric catalytic immunotherapy. Finally, we provide new insights into ultrasound-stimulated nanoparticles for personalized and precision treatment of brain tumors (Fig. 1).

2. Substance transport across the BBB

The BBB is primarily a physical and metabolic barrier that maintains brain homeostasis and prevents the invasion of harmful substances and microorganisms. This is largely due to the tight junctions between endothelial cells in brain capillaries (Fig. 2A and B) [31,32]. Additionally, the BBB contains extensive biochemical barriers, such as tight junction (TJ) proteins and major facilitator superfamily domain-containing 2a (MFSD2A). TJ proteins block the paracellular diffusion of most molecules [33], while MFSD2A regulates cellular endocytosis, forming the BBB's biochemical barrier [34,35]. The brain, being the most energy-demanding organ, relies on a rich capillary network providing approximately 12 m^2 of endothelial surface area for substance exchange [36] and receives about 20 % of cardiac output to maintain normal function [37]. The BBB expresses various receptors and transport proteins that supply the brain with essential amino acids, glucose, iron ions, and low-density lipoproteins [38,39]. Under physiological conditions, substances required by the brain are transported via free diffusion, absorptive transcytosis, receptor-mediated transcytosis (RMT), and carrier-mediated transport (CMT) (Fig. 2C) [40–42].

In pathological conditions, BBB integrity is compromised, leading to increased permeability, microhemorrhages, perivascular deposition of blood-derived products, cellular infiltration, and endothelial cell degeneration [43]. This compromised BBB also offers therapeutic opportunities for brain diseases such as Alzheimer's [43,44], Parkinson's [45], and brain tumors [40]. Both molecular-targeted drugs and nanomedicines can cross the BBB for therapeutic or imaging purposes through: 1) passive targeting, where nanoparticles accumulate in

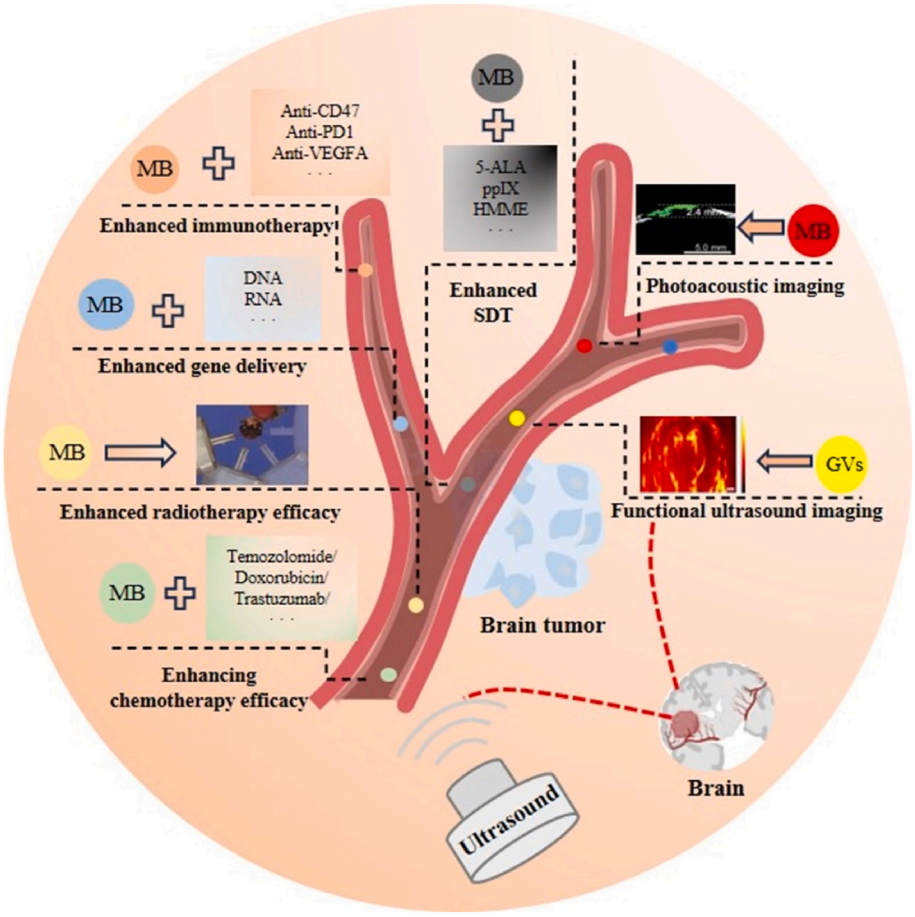

Fig. 1. Schematic diagram of MB-FUS mediated BBB opening for the treatment and imaging of brain tumors; MB-FUS-mediated BBB opening can enhance the efficacy of chemotherapy, radiotherapy, immunotherapy, and SDT, as well as deliver genes for treatment; The imaging guidance of MB-FUS- mediated BBB opening can be achieved by photoacoustic imaging, ultrasound imaging, and so on.

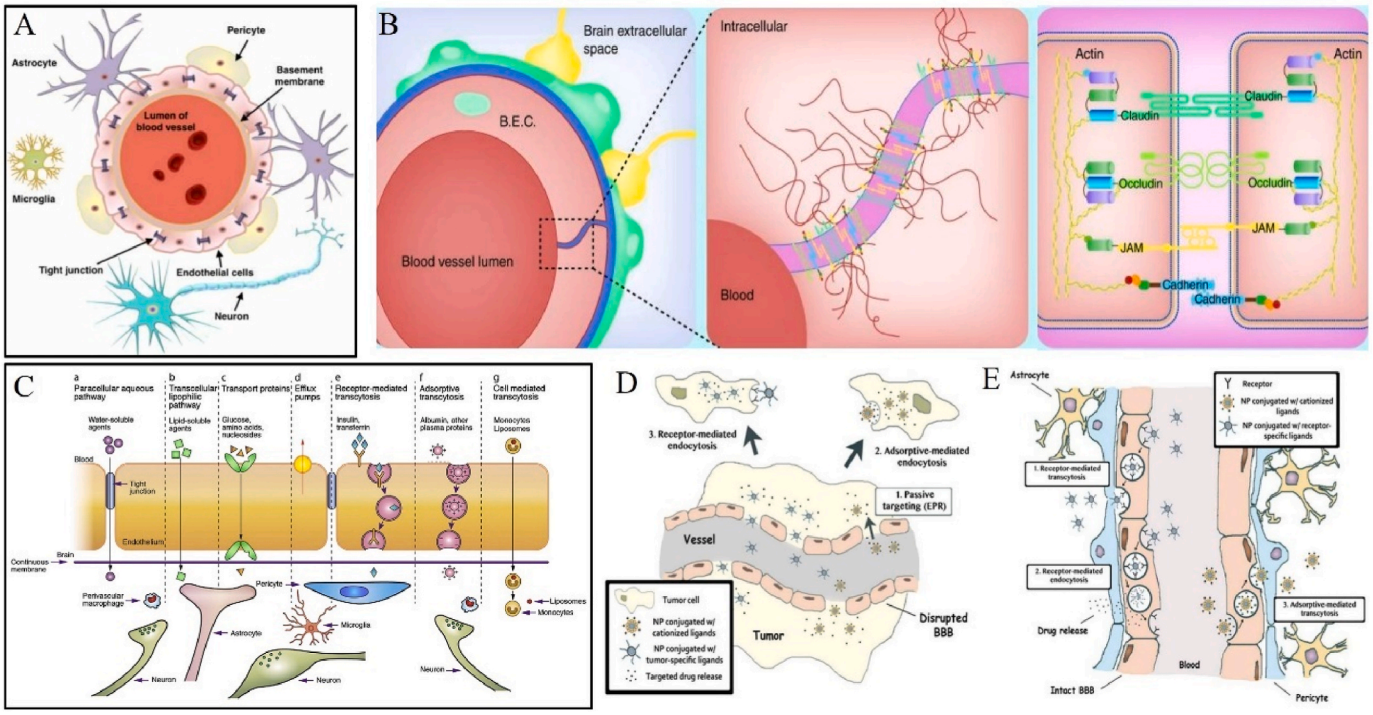

Fig. 2. A) Schematic diagram of BBB, the inner layer of BBB is mainly composed of endothelial cells and tight junctions on the brain capillary wall, while the peripheral cells and matrix are located in the middle layer (i.e., the basement membrane). The outer layer is composed of extracellular matrix and astrocytes [32] *Copyright 2019 Elsevier Ltd*; B) Schematic representation of tight junctions between endothelial cells, tight junction proteins seal the surfaces of adjacent cells together through a complex network of intercellular and extracellular interactions and intracellular anchoring (middle image), and the right image illustrates various tight junction proteins and their intracellular and extracellular interactions in the blood-brain barrier 2015 Future Science Ltd [38] *Copyright 2015 Future Science Ltd.* C) Transport routes across the BBB. Pathways "a" to "f" are commonly for solute molecules; and the route "g" involves monocytes, macrophages and other immune cells and can be used for any drugs or drugs incorporated liposomes or nanoparticles [42] *Copyright 2011 Elsevier B.V.* D) Transport of multifunctional nanoparticles across the BBB:1) passive targeting through EPR effect, 2) adsorption-mediated endocytosis or 3) receptor-mediated endocytosis [48] *Copyright 2013 Elsevier B.V.* D) Mechanisms of transportation across the disrupted BBB and selective targeting of brain tumor cells [48] *Copyright 2013 Elsevier B.V.* 1) receptor-mediated transcytosis; 2) receptor-mediated endocytosis; 3) adsorption-mediated nanometer particles and cationized ligands transcytosis.; Both mechanisms provide targeted delivery to brain cancer cells while sparing normal tissues [48] *Copyright 2013 Elsevier B.V.*

damaged areas via the enhanced permeability and retention (EPR) effect (Fig. 2D) [46,47]; and 2) active targeting, where nanoparticles are modified to bind to receptors or integrins on vascular or tumor endothelial cells (Fig. 2E) [48–50].

3. Research hotspots in brain tumor nanotheranostics

Brain tumors can be broadly classified into primary and secondary brain tumors, with gliomas being the most common primary brain tumors, accounting for approximately 80 % of cases [51–53]. As previously mentioned, the BBB's structure and function are progressively disrupted as brain tumors develop [54]. Although drugs such as temozolomide (TMZ), paclitaxel, and doxorubicin can penetrate the BBB, their penetration and efficacy are limited [55]. However, nanomedicine delivery systems can overcome current BBB limitations [56,57]. Over the past 30 years, research on nanomaterials in brain tumors has steadily increased, with 17,200 publications from January 1994 to March 2024. The United States leads in publications with 7129 articles (41.45 %), followed by China with 3861 articles (22.45 %) (Fig. 3A). Most articles are published in the field of oncology (38.67 %), followed by multidisciplinary sciences and cell biology (9.91 % and 8.34 %, respectively) (Fig. 3B). The paper which published in 2008 is the most cited article, demonstrating that glioblastoma cells secrete exosomes containing mRNA, miRNA, and angiogenic proteins [58]. These exosomes, with their natural BBB-penetrating ability, show great promise as delivery vehicles for therapeutic RNAs and proteins, leading to the development of targeted or modified exosomes for precise brain tumor therapy [59–62].

Similarly, biomimetic systems constructed from tumor or platelet cell membranes can achieve precise drug delivery due to their excellent biocompatibility and ability to prevent drug degradation during delivery [63–65]. Keyword analysis reveals 17 clusters (Fig. 3C), including #0 Case report, #1 brain metastases, #2 brain tumor model, #3 NSCLC patient, #4 blood-brain barrier permeability, #5 brain tumor detection, #6 glioma cell viability, #7 prophylactic cranial irradiation, #8 childhood cancer, #9 hepatocellular carcinoma, #10 prognostic potential, #11 brain cancer incidence, #12 cancer incidence, #13 adult patient, #14 cutaneous melanoma, #15 magnetic field, and #16 glioblastoma multiforme. These clusters can be categorized into brain metastases, brain tumor incidence, and brain tumor therapy. Recent keyword citation bursts (Fig. 3D) show that "deep learning" has the strongest burst intensity (19.27, 2022–2024). Additionally, keywords related to tumor immunity, such as T cells, immune infiltration, immunotherapy, and tumor microenvironment, frequently appear with high burst intensities. This indicates that brain tumor immunotherapy is a current research hotspot, and deep learning-based strategies for brain tumor diagnosis and treatment are also gaining attention.

Under physiological conditions, substances cross the BBB through the aforementioned pathways. Strategies for delivering drugs to the brain using nanomedicines include: 1) modifying the drug surface with receptors highly expressed on cerebrovascular endothelial cells, such as transferrin receptors or lipoprotein receptors (Fig. 4A) [66,67]; 2) using transporter-targeting ligands [68,69] or cationic modifications [70]; 3) employing biomimetic systems to "trick" the BBB into allowing drug delivery (Fig. 4B), such as encapsulating doxorubicin (DOX) in cancer cell membranes for homologous targeting of GBM [71,72]; and 4)

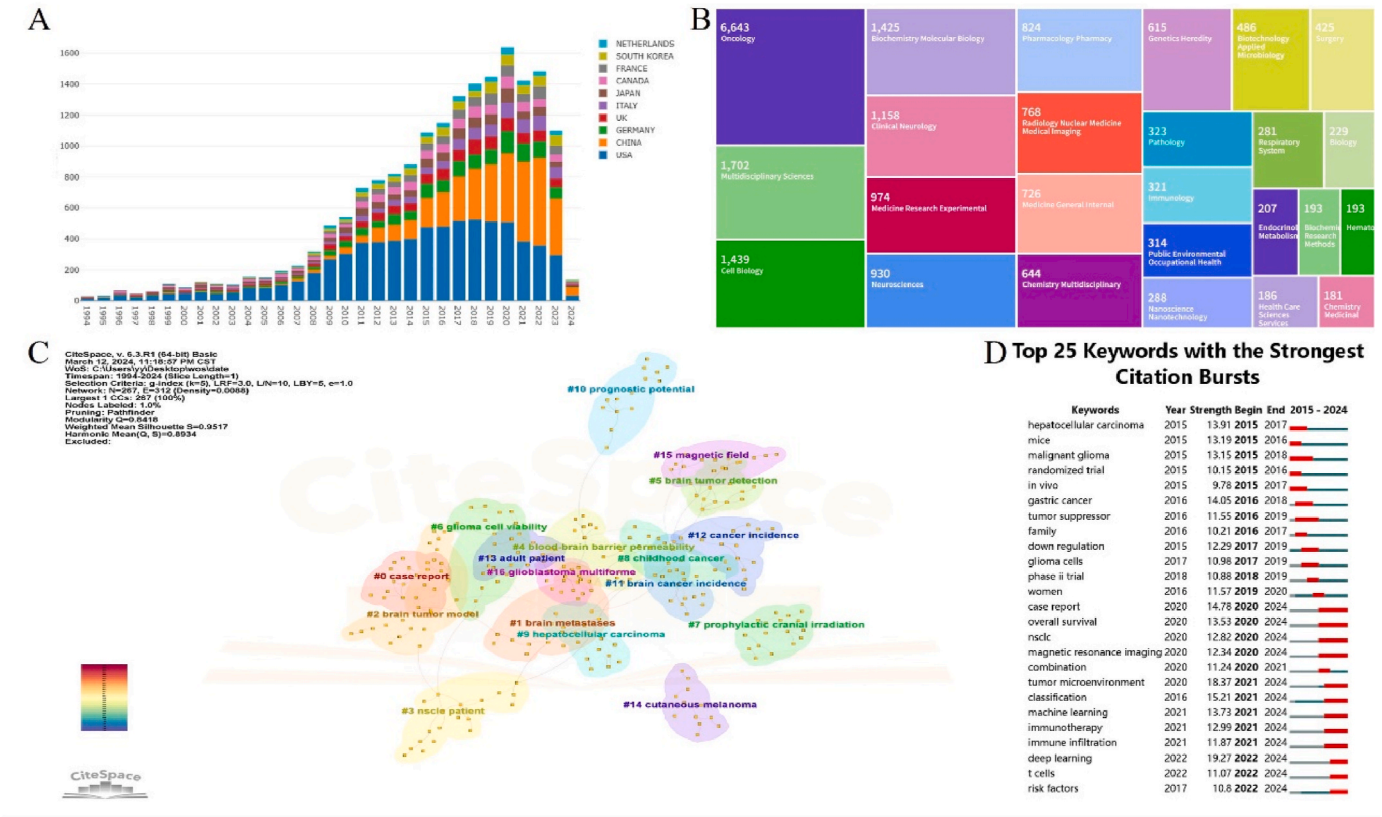

Fig. 3. An analysis of the current status of nanoparticle applications in brain tumors based on bibliometric. A) A quantitative assessment of published articles from 1994 to 2024 reveals the annual trend in publications and the distribution across different countries. B) The top 25 most prolific research areas within this field are identified, highlighting the diverse applications and sub-specializations of nanoparticles in brain tumor research. C) A keyword clustering diagram visualizes the relationships and intersections between the most frequently used keywords. D) An analysis of the top 25 mutating keywords over the past decade provides insights into the evolution of research interests and emerging trends. By identifying keywords that have experienced significant changes in popularity, researchers can stay abreast of the latest developments and adapt their research accordingly.

altering administration routes, such as direct intratumoral injection or intranasal delivery (Fig. 4C) [73]. However, FUS-mediated BBB opening is currently the most widely used method for drug delivery [69], as detailed in the next section (Fig. 4D).

4. MB-FUS-mediated BBB opening

Focused ultrasound (FUS) is an emerging non-invasive diagnostic and therapeutic method that can transiently and targetedly open the BBB in specific brain regions [74]. Initially, ultrasound was used to directly stimulate cerebral blood vessels in targeted areas, but this approach caused unpredictable biological effects, such as intracranial hemorrhage [74,75]. Later, Hynynen and colleagues improved this method by combining low-frequency ultrasound with microbubbles (MBs), proposing a safe and repeatable method for BBB opening [76].

The exact mechanism of MB-FUS mediated BBB opening remains unclear. Studies suggest that the synergistic effect of MBs and ultrasound plays a dominant role. When MBs interact with ultrasound, they may generate acoustic radiation forces, microstreaming, shear stress, and other mechanical effects, reducing the energy required for BBB opening and enhancing the safety of FUS [77,78]. At low ultrasound pressures, MBs undergo stable cavitation, generating shear stress on vascular endothelial cells, particularly during the MB contraction phase. This stress significantly increases and pulls the vascular wall into the lumen, leading to BBB opening [75,79,80]. Additionally, microstreaming around oscillating MBs generates circumferential stress, increasing pressure on microvessels and opening the BBB [81]. Interestingly, mechanical stress from MBs can stimulate ion-sensitive channels on endothelial cell surfaces, further contributing to BBB opening [82]. At high ultrasound pressures, MBs undergo inertial cavitation, with high-speed microjets and localized extreme temperature increases causing BBB opening [81]. Smaller MBs fragment within the lumen, while larger MBs expand and fragment upon contact with the endothelial wall, potentially increasing endothelial cell damage, capillary lumen injury, or red blood cell extravasation (Fig. 5A) [83,84].

Furthermore, MB-FUS interactions can alter BBB structure and cellular pathways. Ultrasound-mediated BBB opening mechanisms may include: 1) transcytosis; 2) endothelial cell cytoplasmic openings, such as fenestration and channel formation; 3) partial opening of tight junctions; and 4) free passage through injured endothelium (Fig. 5B) [75,85]. In the presence of contrast agents (e.g., Optison), ultrasound significantly increases BBB permeability, with reduced mRNA and protein expression of tight junction proteins (claudin-5, occludin, and ZO-1) at 3 h post-stimulation [86]. Additionally, Akt signaling pathway activation in neurons surrounding the BBB increases phosphorylation of downstream signaling molecule GSK3β, reducing interactions between occludin and ZO-1 [87]. MB-FUS can also locally downregulate P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) expression, with P-gp downregulation levels correlating with the extent of BBB opening [88]. This enhances brain penetration of P-gp and BCRP substrate drugs, such as doxorubicin, daunorubicin, vinblastine, vincristine, etoposide, and teniposide [88,89]. After MB-FUS mediated BBB opening, endothelial cells exhibit increased vesicle formation, confirming the presence of cellular transport [85,90].

In summary, MB-FUS mediated BBB opening involves physical effects from MB cavitation and FUS-induced pathway activation, enabling precise control of BBB opening.

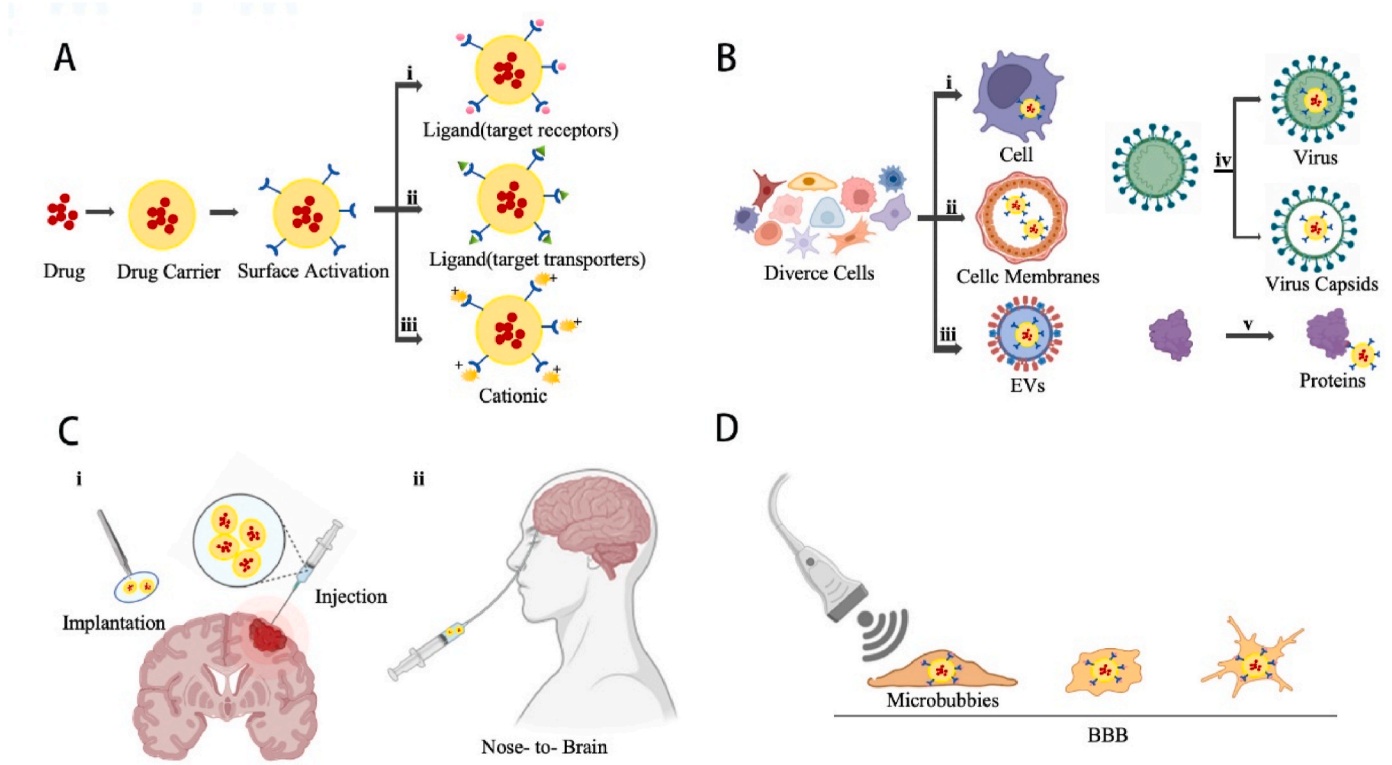

Fig. 4. Redrawn after Qiu et al. [69] *Copyright* 2022 by *the authors*. A) Cross the BBB by surface modification. (i) Schematic of a nanomedicine carrier modified with ligands targeting receptors. (ii) Schematic of a nanomedicine carrier modified with ligands targeting transporters. (iii) Schematic of a nanomedicine carrier modified with cationic. B) Biomimetic nano delivery system that can cheat the BBB. (i) Schematic of cells that can pass directly through the BBB, shown here as a neutrophil. (ii) Schematic of drug carrier coated with cell membrane. (iii) Schematic of extracellular vesicle drug delivery system. (iv) Schematic of virus nano drug delivery system. (v) Schematic of protein-based drug delivery system. C) Bypass the BBB by an unconventional route of administration. (i) Schematic of local administration mode, which can be realized by injection or surgical implantation. (ii) Schematic of nose-to-brain administration mode. D) Schematic of temporary destruction of the blood–brain barrier by ultrasound combined with microbubbles.

5. Parameter control in MB-FUS-mediated BBB opening

Although MB-FUS has largely achieved safe BBB opening, the effects of different FUS parameters, MB types, and doses on the BBB and surrounding brain tissue must be considered [91].

5.1. FUS parameters

Ultrasound frequency largely determines the MB response mode. The frequency range required for BBB opening is 28 kHz to 8 MHz, but due to skull attenuation, the optimal frequency for FUS application is likely between 0.2 and 1.5 MHz [92]. As the mechanical index (MI) increases (0.41–1.38), Evans blue (EB) permeability in the BBB also increases, accompanied by significant red blood cell extravasation [93,94]. FUS exposure below 0.6 MI can induce complete BBB opening without significant red blood cell extravasation or brain injury, while exposure above 0.6 MI is closely associated with cell extravasation (Fig. 6A). Lower ultrasound frequencies result in greater BBB opening (0.4 MHz vs. 1 MHz) (Fig. 6B) [93]. As peak negative pressure (PNP) increases (250, 350, 450 kPa), the number of inertial cavitation events in MBs increases, potentially damaging brain vascular endothelial cells [95]. At 400 kPa PNP, rapid short-pulse (RaSP) sequences do not significantly increase BBB permeability compared to 10 ms tone burst sequences but increase the risk of hemorrhage [96].

5.2. MB parameters

The persistence of BBB opening effects depends on the degradation kinetics of each MB type [94]. Compared to ultrasound parameters, MB parameters are more challenging to evaluate due to the numerous influencing factors in biological systems and the lack of standardized MB preparation and management protocols [91]. MB dose is closely related to BBB opening, with higher MB doses exerting greater force on cerebrovascular endothelial cells under ultrasound radiation, leading to more significant BBB opening [84]. However, MB size, size distribution, and shell composition can also significantly impact BBB opening [97–99]. And gas volume dose in MBs (2 μm and 6 μm in diameter) is the determining factor for FUS (1 MHz, ~0.5 MPa at the focus)-mediated BBB opening, with no significant difference in BBB opening extent under equal volume conditions [100].

In summary, ultrasound amplitude, mechanical index, PNP, and burst duration are related to BBB opening and potential brain tissue injury, while MB type, dose, size, pulse repetition frequency, and total radiation time are related to BBB opening without causing brain tissue damage [93–96,101].

6. Drug delivery for brain tumor therapy following MB-FUS-mediated BBB opening

6.1. Enhanced chemotherapy efficacy

FUS shows great promise in brain tumor therapy, primarily for BBB opening and drug delivery. Postoperative radiotherapy combined with TMZ chemotherapy is the standard treatment for newly diagnosed GBM in adults. Although clinical efficacy is limited, oral TMZ remains the primary treatment for O6-methylguanine-DNA methyltransferase (MGMT)-methylated high-grade gliomas [102].

Preclinical studies have shown that FUS increases local TMZ content in the brain from 6.98 ng/mg to 19 ng/mg and extends TMZ degradation time in the tumor core from 1.02 to 1.56 h [103]. In a rabbit model, one

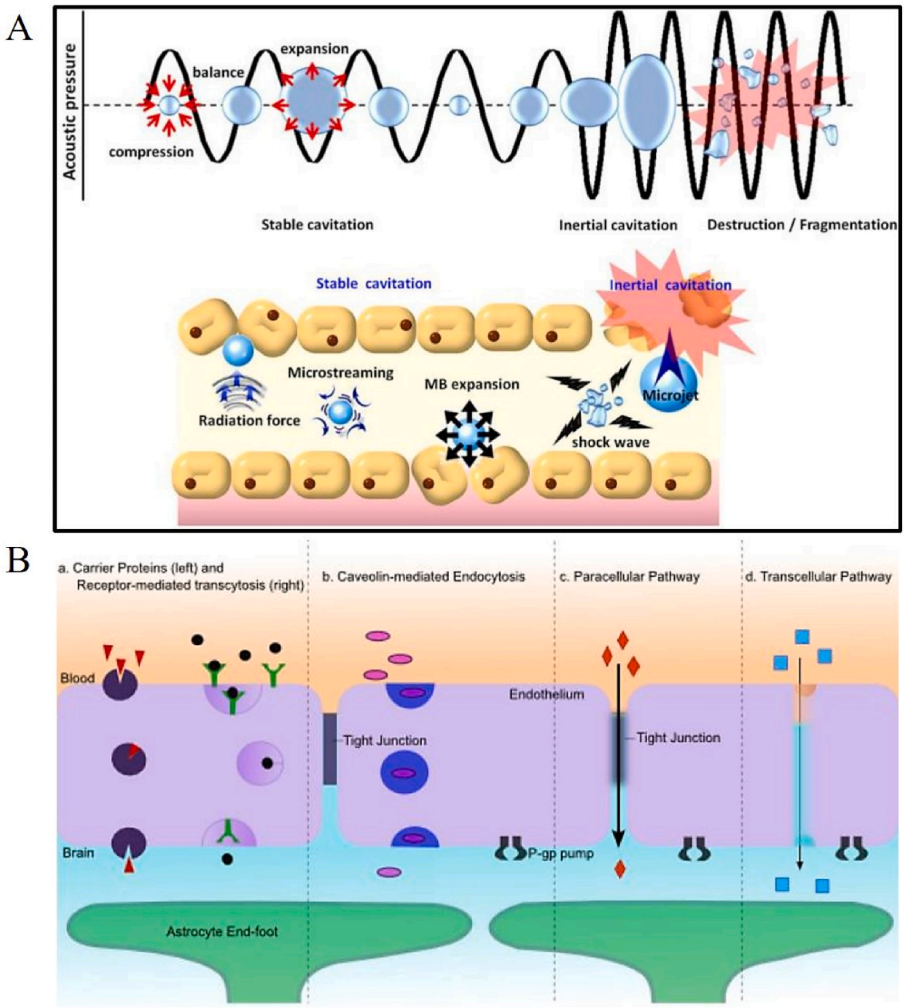

Fig. 5. A) The physical mechanism of induced biological effects when MBs are excited by ultrasonic energy [83] *Copyright 2014 Ivyspring International Publisher*; B) Mechanisms of transport across the BBB following FUS. 4 main methods of transport across the BBB have been identified following FUS-mediated BBB opening. (a) Increased vesicles observed by electron microscopy indicated that transcytosis with either carrier proteins or receptor mediated is upregulated. (b) Caveolin proteins are significantly increased at 1 h after FUS treatment suggesting a role for caveolin-mediated endocytosis. (c) Downregulation of tight junction proteins has shown that paracellular transport can occur following FUS treatment. (d) Cytoplasmic channels created potentially by the fusion of vesicles or damage to the capillary endothelium have been observed using electron microscopy [75] *Copyright 2015 Taylor & Francis.*

hemisphere was treated with FUS for BBB opening, while the contralateral hemisphere served as a control. TMZ and irinotecan (CPT-11) concentrations increased by 21 % and 178 %, respectively, in the FUS-treated hemisphere compared to the control. Drug distribution in the brain was uneven, depending on the distance from the ultrasound source [104].

Scholars have encapsulated doxorubicin in hollow mesoporous organosilica nanoparticles (HMONs) and integrated ultrasmall $Cu_{2-x}Se$ particles on their surface, achieving efficient photoacoustic imaging-guided and ultrasound-responsive in situ brain tumor therapy [105]. Additionally, chemotherapy drugs such as trastuzumab [106,107], bevacizumab [108], methotrexate [109], and carboplatin [110] have been shown to enhance BBB delivery in animal models under ultrasound. MRI can assess BBB opening and its extent. MR-guided FUS (MRgFUS) systems enable precise, safe, and controlled transcranial ultrasound energy delivery, showing great promise in enhancing chemotherapy drug delivery to brain tumors. However, evidence for the safety and efficacy of this treatment in clinical brain tumor patients remains limited [108].

In a phase I, single-arm, open-label study, five glioma patients underwent MRgFUS one day before surgery and received chemotherapy, demonstrating the safety and feasibility of non-invasive low-intensity MRgFUS combined with systemic chemotherapy for transient BBB opening in tumor and peritumoral tissues [111]. However, with the widespread use of TMZ, an increasing number of patients develop drug resistance. NRF2, which enhances drug detoxification, autophagy, DNA repair, and reduces drug accumulation and apoptotic signaling, may reverse TMZ resistance and serve as a new therapeutic target [112].

6.2. *Enhanced radiotherapy efficacy*

Postoperative radiotherapy is a conventional therapy for brain tumors, but few studies have examined whether radiotherapy affects FUS-mediated BBB opening. Scholars administered a total dose of 30 Gy in five fractions to one hemisphere of normal mice and performed FUS on days 2 (acute phase) and 30 (chronic phase) post-radiotherapy [113]. Radiotherapy did not affect FUS-mediated BBB opening but facilitated BBB opening during the acute phase. Radiotherapy alone caused mild BBB opening, while FUS following radiotherapy increased peak fluorescence intensity of hypertonic dye in the ultrasound region by 17.5 ± 12.1 % compared to FUS alone, suggesting that radiotherapy may sensitize FUS-mediated BBB opening [114]. Interestingly, a study first combined radiotherapy and FUS in an orthotopic GBM mouse model. Local MB-FUS was performed to open the BBB before radiotherapy,

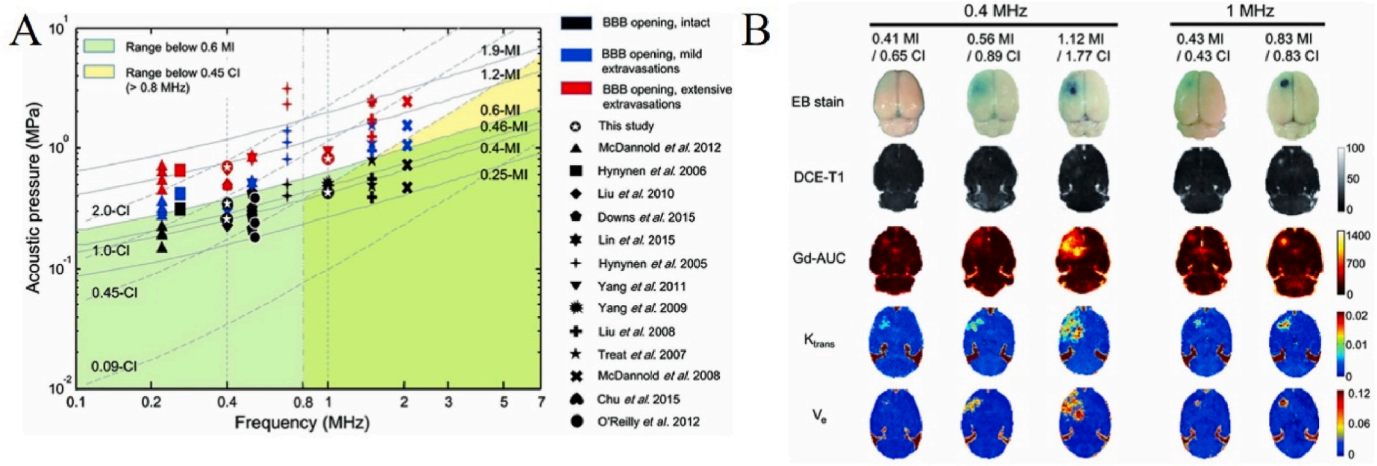

Fig. 6. A) FUS-induced BBB opening of the previously employed exposure levels on the iso-contour MI/CI lines and denoted as three different levels: intact (marked in black), mild erythrocyte extravasations (marked in blue), and severe erythrocyte extravasations/brain damages (marked in red). FUS exposure levels within the range below 0.6-MI (green area) and below 0.45-CI (above 0.8 MHz, yellow area) seemed to induce intact BBB-opening without significant erythrocyte extravasations or brain damage [93] *Copyright 2016 The Author(s).* B) Representative gross views of EB-stained brains and post-processed DCE-MRI parameters including the signal-intensity (SI) maps, Gd-based area-under-curve (Gd-AUC) maps, Ktrans maps, and Ve maps at various MI/CI exposure levels. The scale of BBB-opening increases with MI/CI for both the 0.4-MHz FUS group and the 1-MHz FUS group. The mild BBB-opening caused by low MI/CI with 1-MHz FUS was similar to the BBB-opening of low MI/CI 0.4-MHz FUS. The higher MI/CI 0.4-MHz FUS and higher MI/CI 1-MHz FUS induced aggressive BBB-opening accompanied by erythrocyte extravasations. The FUS dimension is larger in 0.4-MHz than in l-MHz, therefore 0.4-MHz exposure contributed to a larger BBB-opening dimension [93] *Copyright 2016 The Author(s).* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

followed by radiotherapy 2 h later [115]. The RT-FUS (2 Gy) group had a significantly longer median survival than the RT (2 Gy) alone and control groups ($P < 0.05$) but did not exceed the RT (5 Gy) group. Later, they treated six patients with recurrent malignant high-grade gliomas with RT-FUS. Three patients achieved stable disease (average 323 days) with or without salvage chemotherapy or targeted therapy, and one patient showed partial response after RT-FUS, with an objective response rate (ORR) of 16.7 %. This clinical trial (NCT01628406) demonstrated the safety of RT-FUS combination therapy.

6.3. Enhanced gene delivery

DNA, as a natural biomaterial, has low cytotoxicity, immunogenicity, biosafety, high specificity, and tunability, making it a promising smart biomaterial [116,117]. By constructing pH-responsive DNA octahedron loaded with epirubicin (Epr@DNA-Octa) and enhanced its delivery to the brain using MB-FUS, significantly improving the survival of brain cancer mice [118]. A gene-liposome system has been developed, in which liposomes carrying plasmid DNA (pDNA) formed

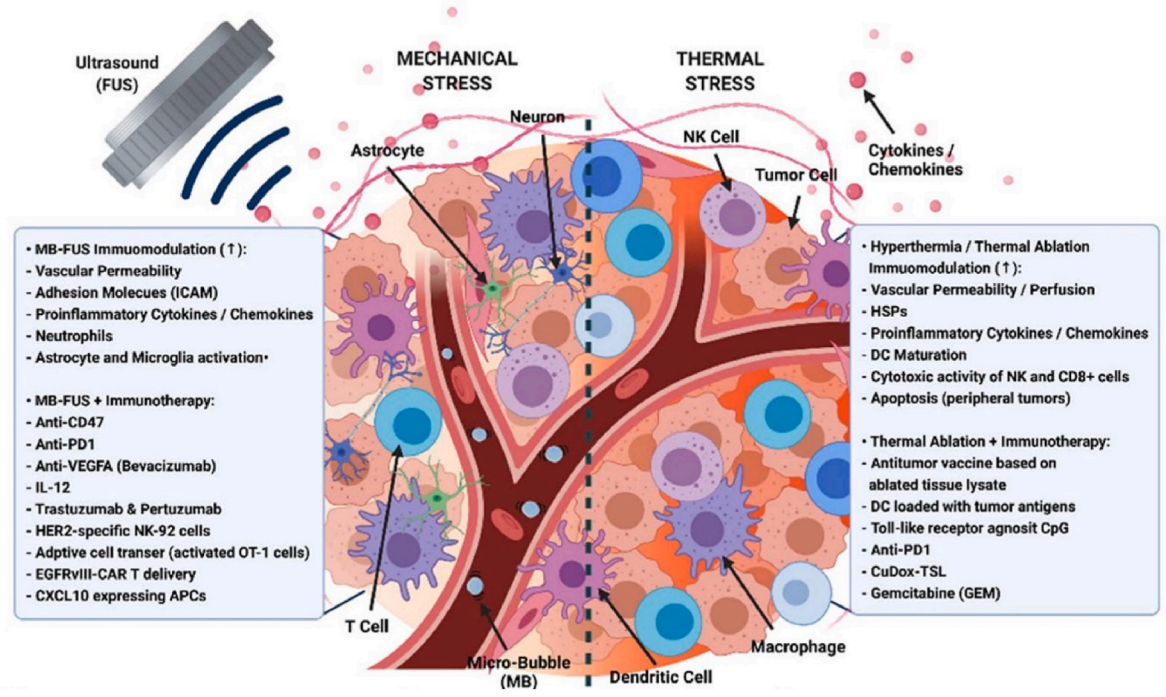

Fig. 7. Schematic highlighting the immunomodulatory mechanism of thermal and mechanical stress and the most promising combinations with immune adjuvants to treat brain tumors [124] *Copyright 2022 The Author(s),.*

liposome-plasmid DNA (LpDNA) [119]. FUS treatment enhanced CNS gene expression, with transfection efficiency dependent on LpDNA dose. Higher pDNA payloads resulted in higher transfection rates. Intranasal administration of plasmid DNA nanoparticles (NPs) offers a new approach for brain disease treatment. With FUS assistance, transgenic expression increased in the treated brain hemisphere, altering cell transfection patterns at the ultrasound site and improving plasmid nanoparticle penetration into the brain parenchyma [120].

In summary, MB-FUS- guided DNA [118–121] and RNA [122,123] delivery is a safe and non-invasive brain-targeted gene therapy strategy.

6.4. Enhanced immunotherapy

MB-FUS-mediated BBB opening can modulate the brain tumor immune microenvironment through mechanical and thermobiological effects, transforming low immune cell-infiltrated tumors into high immune cell-infiltrated tumors, potentially leading to long-term antitumor immune responses (Fig. 7) [124]. During the acute phase of MB-FUS -mediated BBB opening, microglia, astrocytes, and T and B lymphocytes are recruited in response to vascular changes, triggering a mild inflammatory response through upregulation of PDGFRβ and VEGF-A [125]. Repeated ultrasound stimulation may increase the expression of genes related to pro-inflammatory cytokine and chemokine signaling and dendritic cell changes, promoting the generation of pro-inflammatory cytokines, chemokines, and trophic factors (CCTFs). This shifts tumor-associated macrophages (TAMs) and microglia toward a pro-inflammatory phenotype, remodeling the tumor microenvironment (TME) and overcoming immune evasion in GBM [126]. Single-cell sequencing confirmed that MB-FUS- mediated BBB opening remodels the TME by recruiting CNS-associated macrophages (CAMs) and proliferating microglia, along with changes in disease-associated microglial populations [127].

Combining MB-FUS with immune checkpoint inhibitors and/or adoptive cell therapy can induce robust responses. The study successfully delivered anti-PD-1 using MB-FUS, accumulating it within gliomas and enhancing the focal delivery and persistence of chimeric antigen receptors in the brain, significantly improving mouse survival [128]. Delivering PD-1 inhibitors (PD-1-IN-17) significantly increased $CD4^+$ and $CD8^+$ T cell infiltration [129]. However, anti-PD-1 therapeutic activity may be mediated by M1-like polarization of microglia in the brain TME [130]. Researchers have constructed an antibody-drug conjugate (T-DM1) for treating breast cancer brain metastases. MB-FUS alleviated the vascular barrier and enhanced interstitial convective transport in solid tumors, increasing T-DM1 delivery to tumor sites [131]. When combined with other immune modulators (e.g., monoclonal antibodies, immune cells, and cytokines) that do not readily accumulate in the brain, MB-FUS can serve as a powerful adjuvant therapy, as indicated by a recent review [132]. In a preclinical study, a combination of FcE-aCTLA-4, anti-PD-1, and doxorubicin with MB-FUS achieved a 90 % cure rate in an immunotherapy-resistant glioma mouse model, associated with robust $CD8^+$ T cell infiltration and immune memory establishment. This team's clinical trial (NCT05864534) showed that combining anti-PD-1, doxorubicin, and MB-FUS significantly upregulated FcγRIIIA on TAMs, enhancing immunotherapy efficacy [133]. In summary, MB-FUS-mediated BBB opening enhances immunotherapy efficacy by delivering immune inhibitors or remodeling the TME.

6.5. Enhanced SDT

Reactive oxygen species (ROS) play a significant role in cancer therapy. Low ROS levels regulate immune cells in the TME and are involved in glioma cell proliferation, invasion, metastasis, and death [134]. ROS accumulation can lead to glioma cell death [135]. The combination of ultrasound and sonosensitizers under certain conditions generates large amounts of ROS, known as SDT, which has been explored as a promising alternative for glioma treatment [136,137]. SDT mechanisms may involve low-energy ultrasound and sonosensitizer-mediated cavitation, followed by sonomechanical and/or sonochemical processes that initiate cell damage [138]. For example, ultrasound-excited TiO_2/PEG polymers induce glioma cell death through physical membrane disruption rather than oxygen radical damage [139]. SDT also reduces mitochondrial membrane potential [140], disrupts calcium ion balance across cell membranes [141], and activates death receptor pathways [142] to trigger cancer cell death. However, traditional sonosensitizers, such as 5-ALA [143], protoporphyrin IX (ppIX) [144], hematoporphyrin monomethyl ether (HMME) [145,146], and fluorescein [147], lack specific targeting and are hindered by the BBB, limiting their tumor-killing efficacy [148]. Researchers have modified sonosensitizers with tumor-homing peptides [149], angiopep-2 [27], and exosome camouflage [137], successfully delivering them to brain tumor regions with MB-FUS assistance and achieving efficient SDT under repeated ultrasound stimulation (Fig. 8A–C) [27]. Traditional sonosensitizers have limited ROS generation under ultrasound, resulting in suboptimal SDT efficacy. Therefore, exploring new sonosensitizers with higher ultrasound responsiveness is crucial. Promising candidates include piezoelectric materials, defective semiconductors, hybrid-assembled polymers with narrow bandgaps, and novel sono-catalysts with heterojunctions [150]. Recent studies have shown that TMZ can generate ROS under ultrasound, enhancing SDT and TMZ chemotherapy efficacy in GBM [151].

Piezoelectric materials, such as P(VDF-TrFE) [152,153] and BaTiO3 [154], can also serve as sonosensitizers for glioma treatment. In MB-FUS- mediated delivery, layered piezoelectric $SrBi_2Ta_2O_9$ nanoparticles (SBTO NPs) selectively accumulate in mitochondria. Under ultrasound, piezoelectric materials undergo electron-hole pair separation, generating charges that indirectly reduce mitochondrial membrane potential through ROS or directly depolarize mitochondria, inducing apoptosis [155]. In our recent review, we termed this ultrasound-triggered piezoelectric material-mediated ROS generation or electrical stimulation for tumor treatment as sono-piezo dynamic therapy (SPDT) [156]. Importantly, ultrasound-excited P(VDF-TrFE) nanoparticles can trigger microglial polarization toward the M1 phenotype, disrupting the immunosuppressive GBM microenvironment and enhancing immunotherapy efficacy [157]. This therapeutic strategy is referred to as piezoelectric catalytic immunotherapy.

In summary, SDT has been demonstrated as a promising alternative for brain tumor treatment. Optimizing sonosensitizers, such as using piezoelectric materials, can further enhance therapeutic efficacy. SPDT, combining ultrasound and piezoelectric materials, can sensitize GBM to piezoelectric catalytic immunotherapy.

6.6. Other applications

With the advancement of precision medicine, theranostics has become a research hotspot. By incorporating MnO_2 [158], DOTA-Gd [152], and superparamagnetic iron oxide [159], MRI-guided MB-FUS therapy for brain tumors can be achieved. Additionally, combination therapies can adapt to the complex TME. For example, Scholars used HMME to mediate both photodynamic therapy (PDT) and SDT, generating more ROS for C6 glioma cell inactivation [146]. Other studies have combined chemotherapy drugs, such as TMZ [160], bleomycin (BLM) [161], and DOX [162], with SDT for brain tumor treatment, achieving promising results. Interestingly, combining SDT with autophagy, thermotherapy, gas therapy, and immunotherapy shows great potential for brain tumor treatment (Fig. 8D) [148]. Current clinical studies on FUS for brain tumor treatment are detailed in recent reviews [163].

7. Ultrasound-responsive nanoparticles for brain tumor imaging

Ultrasound imaging, with its real-time and repeatable operation advantages, has long been used in neurosurgical imaging [164]. However, MRI and positron emission tomography (PET) imaging,

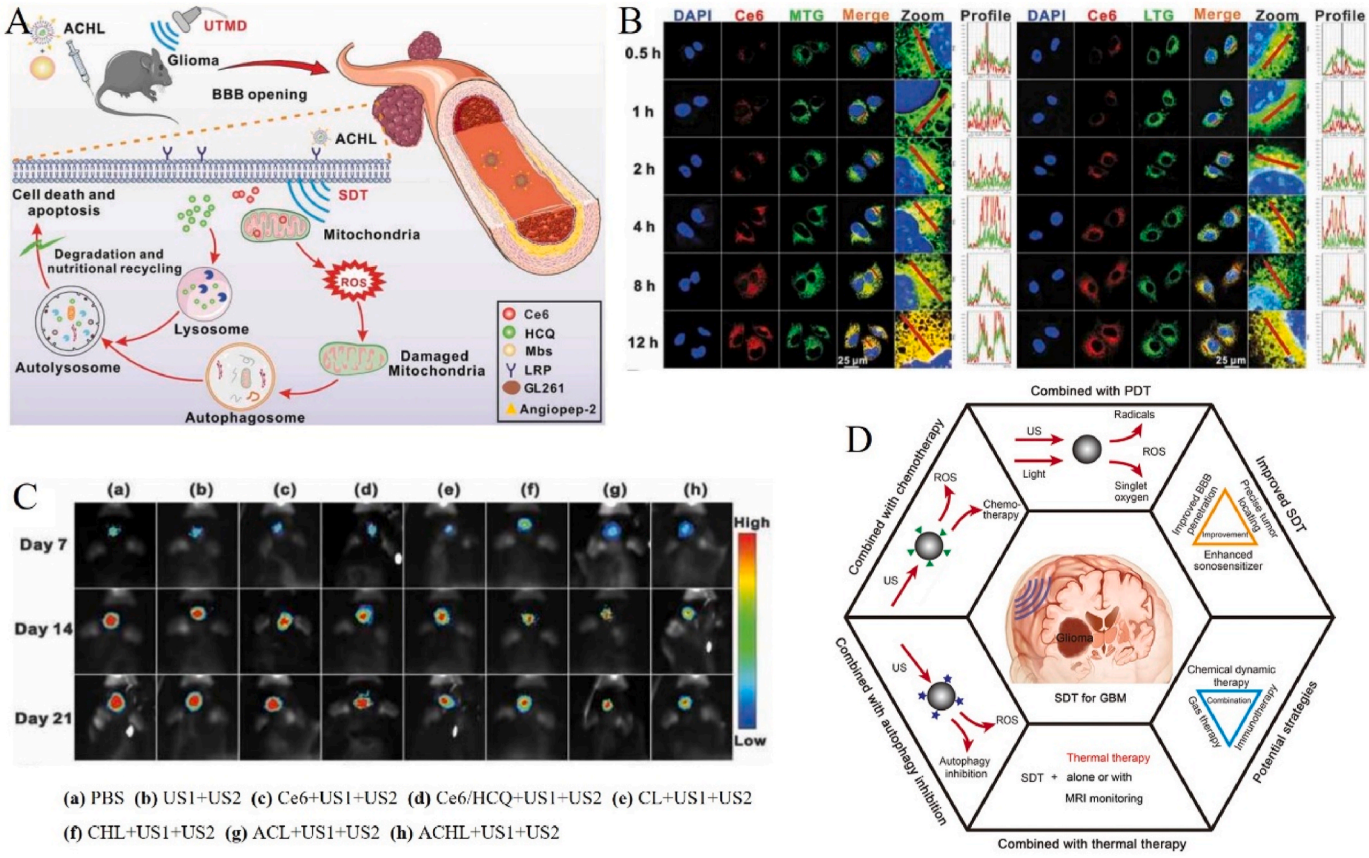

Fig. 8. A) A schematic illustration depicts the delivery of the sonosensitizer Ce6 and the autophagy inhibitor HCQ to brain tumors, modified with Angiopep-2, to enhance the anti-glioma effects of SDT through autophagy inhibition [27] *Copyright 2019 Taylor & Francis.* B) Ce6 preferentially accumulates in mitochondria [27] *Copyright 2019 Taylor & Francis.* C) Bioluminescence signals associated with tumor growth over time [27] *Copyright 2019 Taylor & Francis.* D) A schematic representation of SDT strategies employed for the treatment of GBM multiforme [148] *Copyright 2022 The Author(s).*

particularly perfusion MRI, provide physiological information about brain tumors and are increasingly important in glioma response assessment [165]. A clinical study comparing intraoperative enhanced MRI and intraoperative contrast-enhanced ultrasound (CEUS) for GBM location, morphology, margins, and size found that intraoperative CEUS had similar enhancement patterns to intraoperative enhanced MRI, suggesting its potential as an intraoperative imaging aid for GBM [166].

MRgFUS is an emerging technology that enables controlled and safe BBB disruption in time and space. MRgFUS systems can also monitor the biological effects of ultrasound energy delivered to the CNS in real time, measuring local thermal effects or acoustic emissions from oscillating microbubbles [108]. Preclinical and clinical studies have confirmed that MB-FUS-mediated BBB opening under MRI guidance and monitoring enhances the delivery of traditional chemotherapy drugs or novel nanocarriers designed for active drug transport or extended drug half-life, significantly improving therapeutic efficacy [167,168]. However, MRgFUS requires patients to be placed inside an MRI scanner, and the imaging time for precise targeting is lengthy (over 3 h), which may be challenging for elderly patients. The high cost also limits the application of various treatment methods [169].

Neuronavigation-guided real-time passive acoustic mapping can accelerate FUS procedures without MRI by visualizing acoustic events in the brain to confirm targets and monitor treatment at different locations [169]. The NaviFUS system has a BBB opening dose tolerance of less than 0.68 MI, with no surgery-related adverse events or radiological sequelae. The device is portable, integrated with standard neuronavigation systems, and does not require large spaces or expensive intraoperative MRI suites. The procedure is efficient and can be completed in 15 min. NaviFUS does not require rigid skull fixation and achieves target accuracy with less than 3 mm deviation error [170]. At higher FUS levels (MI = 0.81), immunomodulatory responses may convert "cold" tumors to "hot" tumors, supporting NaviFUS advancement to the next stage of clinical trials [171]. Under neuronavigation guidance, FUS-induced BBB opening enables "bidirectional transport" between the brain and bloodstream, releasing brain tumor-derived biomarkers into the blood. Analysis of blood samples collected before and after FUS sonication showed that ultrasound biopsy enriched plasma circulating tumor DNA (ctDNA), with mononucleosome-free DNA (cfDNA) fragments (120–280 bp) increasing up to 1.6-fold, achieving ultrasound biopsy of high-grade gliomas under neuronavigation guidance for the first time [172]. However, spatial cavitation monitoring is crucial for neuronavigation-guided FUS. By developing a real-time cavitation mapping, enabling full burst analysis for neuronavigation-guided FUS systems with enhanced spatial resolution, confirming the feasibility of real-time acoustic mapping for safe and efficient BBB opening [173].

Ultrasound imaging-guided MB-FUS-mediated BBB opening primarily uses microbubbles, phase-shift emulsions, and gas-filled nanobubbles, which form microbubbles or gasify under ultrasound, enabling contrast-enhanced ultrasound imaging [174]. A novel protein nanoparticle for molecular imaging is the gas vesicle (GV), a gas-filled protein nanostructure expressed by certain cells [175]. Scholars have showed that intravenous infusion of GVs enhances ultrafast Doppler ultrasound contrast and visually evoked hemodynamic contrast in transcranial functional ultrasound imaging (fUS) in mice, reliably amplifying neuroimaging signals (Fig. 9A and B) [176]. Ultrasound imaging also provides opportunities for anatomical structure visualization, blood flow imaging, cavitation imaging, tissue property measurement, and

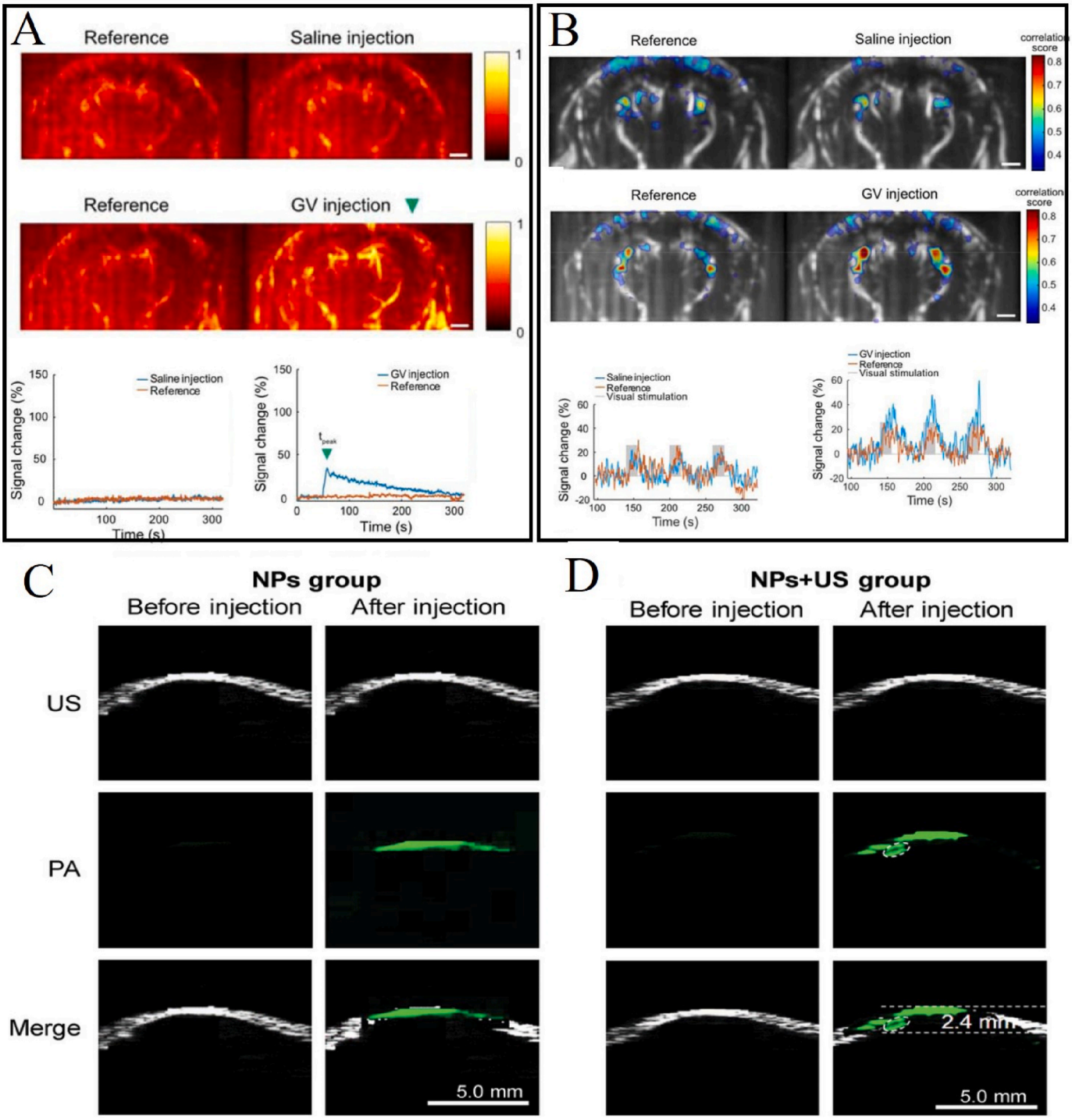

Fig. 9. A) Power Doppler images at 60s with and without saline and GV injection; Mean brain signal change over time with and without saline and GV injection [176] *Copyright 2019 The Authors.* B) Activation maps overlaid on power Doppler images of the mouse brain with and without bolus injection of saline and GVs; fUS signals in the most responsive LGN pixel with and without bolus injection of saline and GVs [176] *Copyright 2019 The Authors*. C) Microscopic ultrasonic and PAI results of brain tumors before and after treatment with PBT NPs alone [182] *Copyright 2019 Wiley-VCH.* D) Microscopic ultrasonic and PAI results of brain tumors before and after the combined therapy of PBT NPs and FUS coupled with intravenous microbubble injection [182] *Copyright 2019 Wiley-VCH.*

temperature monitoring, as indicated by a recent review [177].

Photoacoustic imaging (PAI) combines the high selectivity of optical imaging with the deep penetration of ultrasound imaging. Scholars synthesized mesoionic dye A1094 encapsulated in Arg-Gly-Asp-modified hepatitis B virus core protein for effective second near-infrared window (NIR-II) PAI of brain gliomas, achieving an imaging depth of 5.9 mm and high-resolution PAI images, precisely co-localized with ultra-sensitive single-photon emission computed tomography images [178]. In addition, scholars have constructed indocyanine green (ICG)-doped microbubbles (MBs-ICG) for visualizing FUS-mediated BBB opening and enhancing photothermal therapy (PTT) for GBM [179]. MBs-ICG combined with FUS achieved in situ and synchronous visualization of BBB opening with a NIR-II fluorescence signal-to-noise ratio of 6.2 ± 1.2, providing a new method for monitoring BBB opening and

enhancing GBM treatment. Among various NIR-II fluorescent nanoprobes, aggregation-induced emission (AIE) has gained attention for its fluorescence enhancement at high concentrations or in aggregated states, overcoming the limitations of traditional organic dyes' aggregation-caused quenching effects [180]. Several studies have achieved NIR-II imaging based on AIE dots, with large near-infrared absorption rates promoting near-infrared photoacoustic imaging, enabling in situ brain tumor NIR-II and PAI multimodal imaging (Fig. 9C and D) [180–183]. Additionally, by constructing a hybrid cell membrane-coated ICG liposomes (HM-Lipo-ICG) as biomimetic near-infrared (NIR) fluorescent probes, achieving a signal-to-noise ratio of 6.5 in the GBM region of an orthotopic glioma mouse model under high-contrast NIR imaging guidance, improving tumor margin detection accuracy by fourfold [184].

8. Inflammatory responses during MB-FUS-mediated BBB opening

MB-FUS-mediated BBB opening facilitates drug delivery but may also allow exogenous toxins and pathogens to enter the brain, causing inflammatory responses [185]. Previous studies have shown that MRgFUS-induced BBB opening can cause sterile inflammation in the

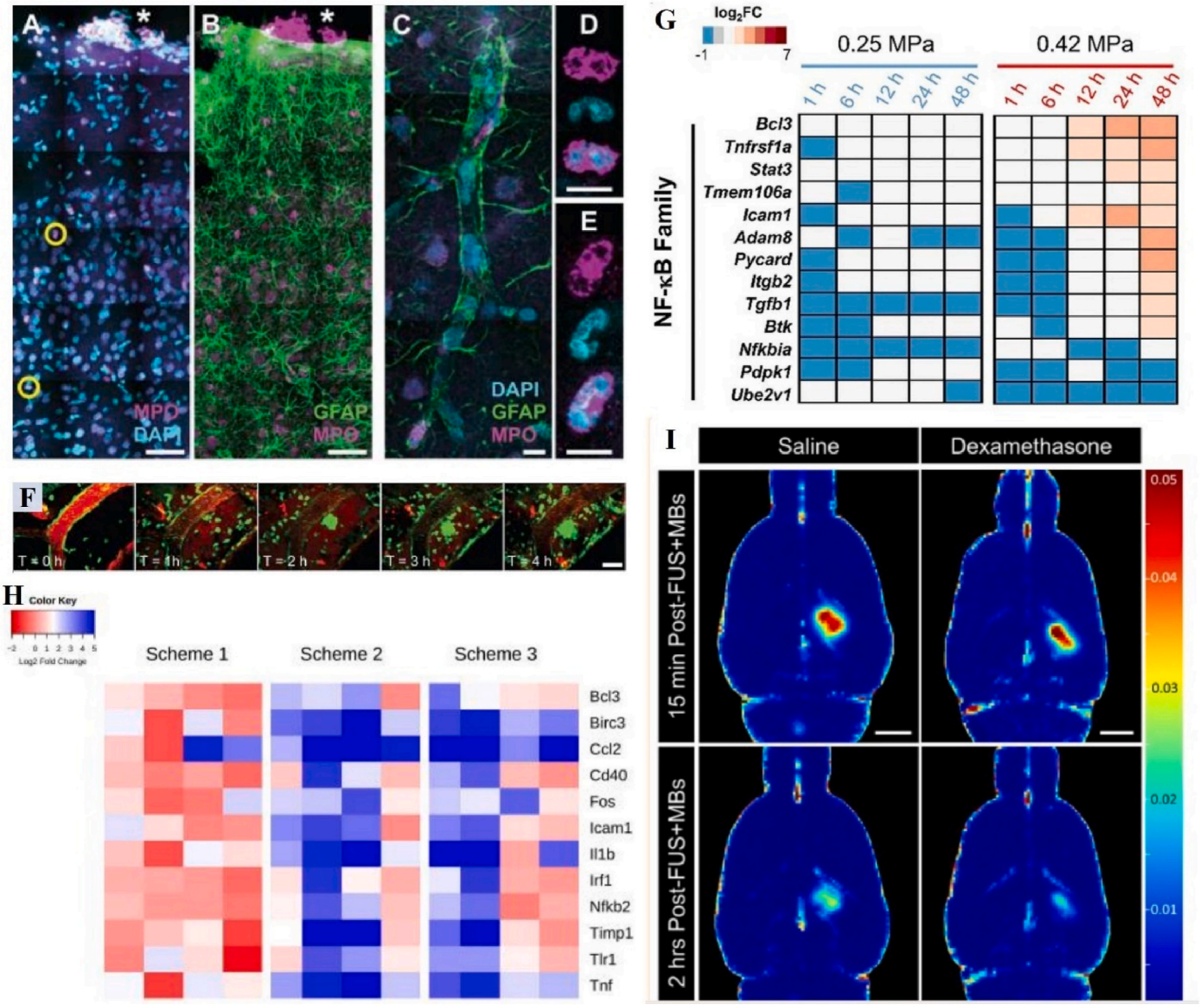

Fig. 10. (A, B) Brain sections were stained for neutrophils (MPO, magenta), astrocytes (GFAP, green), and nuclei (DAPI, cyan). Numerous MPO + neutrophils were present in the dura (*), in both sonicated and control animals, likely due to the cranial window procedure. (C–E) Neutrophils were found within and outside of blood vessels [188] *Copyright 2021 The author(s).* (C) A blood vessel is outlined by GFAP+ (green) astroglial processes [188] *Copyright 2021 The author(s).* (D, E) Neutrophils were identified as MPO+ (magenta) cells containing multi-lobed nuclei (counter-stained with DAPI, cyan) [188] *Copyright 2021 The author(s).* F) A mass of cells began to accumulate adjacent to an affected arteriole at T = 1 h after the onset of sonication, and increased in volume until the end of imaging [188] *Copyright 2021 The author(s).* G) Heat map of genes associated with the inflammatory response at 0.25 MPa (blue line) and 0.42 MPa (red line) [189] *Copyright 2022 The Author (s).* H) Heat map of genes displaying significant changes in expression relative to control regions 6 h post-FUS. Scheme 1. MB Dose: 10(μl Definity/kg), PNP: acoustic controller used, PRF: 1(Hz), Pulse Length:10 (ms), Sonication Duration: 120(s); Scheme 2. MB Dose: 100(μl Definity/kg), PNP: 0.290, PRF: 1(Hz), Pulse Length:10 (ms), Sonication Duration: 120(s); Scheme 3. MB Dose: 100(μl Definity/kg), PNP: acoustic controller used, PRF: 1(Hz), Pulse Length:10 (ms), Sonication Duration: 120(s) [190] *Copyright 2017 Ivyspring International Publisher.* I) Representative K^{trans} maps acquired at 15 min and 2 h post-FUS + MB exposure demonstrate a more rapid restoration of BBB integrity in a DEX-treated animal compared to a saline-control animal [193] *Copyright 2020 The Author(s).* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

normal brain microenvironment [186]. Glioma implantation also increases monocytes, neutrophils, and lymphocytes in the brain parenchyma. Transient BBB opening using MRgFUS combined with microbubbles can activate monocyte homing and differentiation, inducing a shift toward a more pro-inflammatory state in the glioblastoma immune environment [187]. MB-FUS-mediated BBB opening can cause acute inflammatory responses characterized by transient upregulation of pro-inflammatory genes. The study identified leukocyte activity indicators during the acute inflammatory phase after ultrasound treatment, including transendothelial migration, cell aggregate formation, and cell clusters capable of disrupting blood flow, with neutrophils being the most critical leukocyte type (Fig. 10A–F) [188]. Scholars have identified sterile inflammation as a potential biological effect accompanying MB-FUS-mediated BBB opening, as even the lowest acoustic settings causing BBB permeability could induce sterile inflammation [186]. However, at low ultrasound frequencies (0.25 MPa), BBB opening did not cause cell/tissue damage or sterile inflammation, while at 0.42 MPa, BBB opening could induce sterile inflammation, indicating that ultrasound parameters influence sterile inflammation occurrence (Fig. 10G) [189]. Additionally, they found that A2-type astrocyte expression has neuroprotective properties, promoting brain tissue repair and maintaining brain microenvironment homeostasis. Microbubble dose is also related to sterile inflammation. At clinical imaging doses, genes involved in acute inflammation and immune activation, such as NFκB signaling pathway genes, did not significantly change. However, at high MB doses, the NFκB signaling pathway was activated, accompanied by edema, neuronal degeneration, neutrophil infiltration, and microhemorrhage (Fig. 10H) [190]. A useful indicator during MB-FUS-mediated BBB opening is microbubble cavitation dose, as it provides real-time information on biological effects [191]. In the context of target cavitation doses, as cavitation dose increases (1×10^7 V^2•s, 5×10^7 V^2•s, 1×10^7 V^2•s), the relative gene expression of inflammatory cytokines and receptors also significantly increases, but all cavitation dose groups return to baseline gene expression levels at 72 h. Therefore, cavitation monitoring and control during MB-FUS-mediated BBB opening can potentially modulate or limit the extent of neuroinflammation [192].

Administering dexamethasone 24 h after MB-FUS-mediated BBB opening can accelerate BBB recovery and reduce the risk of inflammation-induced tissue damage (Fig. 10I) [193]. In summary, MB-FUS- mediated BBB opening is a safe and effective strategy for brain tumor therapy, as indicated by a recent review [194].

9. Outlook

MB-FUS-mediated BBB opening for drug delivery shows great promise in brain tumor therapy, although it may induce sterile inflammatory responses [186]. However, scholars have constructed a neutrophil (NE) membrane-like system loaded with doxorubicin, which has similar inflammatory chemotaxis to mature NEs [195]. This system can move along chemokine gradients to residual GBM sites post-surgery, achieving targeted drug delivery and treatment. Therefore, leveraging inflammatory factors generated during MB-FUS-mediated BBB opening to create favorable targets for brain tumor immunotherapy is promising but challenging. This process requires careful consideration of MB-FUS-mediated BBB opening safety, ensuring no damage to normal brain tissue or significant red blood cell extravasation. Most published clinical studies on FUS-mediated BBB opening for enhanced brain tumor therapy are phase 0 or I trials, focusing on assessing the safety and feasibility of FUS-mediated BBB opening. Seven clinical trials (involving 61 patients) have shown that FUS is a promising strategy for safely disrupting the BBB, enabling precise and non-invasive lesion targeting, and enhancing drug delivery [196]. FUS-mediated BBB opening has demonstrated significant safety and potential for enhancing drug delivery in patients with malignant gliomas and recurrent GBM, making it a safe and feasible method for improving brain tumor treatment outcomes [197]. To date, no clinical trials have formally disclosed or reported the efficacy of FUS-mediated BBB opening for brain tumor treatment. However, this therapy's potential clinical advantages, such as minimal invasiveness and benefits for pediatric patients, are highly innovative. After confirming the efficacy of FUS-mediated BBB opening for brain tumor treatment, the next research direction may be optimizing FUS parameters to enhance therapeutic effects, including adjusting FUS stimulation frequency and targets based on BBB or BTB characteristics [198].

MB-FUS-mediated BBB opening enhances chemotherapy, radiotherapy, gene therapy, and SDT efficacy. SDT, through ROS-induced glioma cell damage, is considered a promising alternative for glioma treatment [136,137]. However, existing sonosensitizers, mostly derived from photosensitizers, have limited ROS production [199]. Therefore, developing new sonosensitizers for brain tumor treatment is attractive. Our team [152,156,200] has used piezoelectric materials as sonosensitizers for glioma and 4T1 cell SDT, achieving promising results. We termed this approach SPDT, where ultrasound triggers electron-hole pair separation in piezoelectric materials, inducing immunogenic cell death (ICD) through piezoelectric electrical stimulation and ROS. This strategy shows great potential in glioma treatment, as ROS-mediated ICD can promote TAM polarization toward the M1 phenotype, remodeling the TME. The mechanism may involve NF-κB pathway activation [201] or targeting lactate in the TME. Lactate, upon receiving H+, converts to pyruvate, reducing lactate accumulation in tumor cells and effectively disrupting the immunosuppressive microenvironment, thereby enhancing immunotherapy efficacy [202]. In summary, MB-FUS- mediated BBB opening, combined with piezoelectric materials, can enhance TME remodeling through piezoelectric electrical stimulation and ROS-mediated ICD, sensitizing brain tumors to immunotherapy. This requires further preclinical validation.

MB-FUS-mediated BBB opening has immense potential in brain tumor therapy but faces challenges in safety, technical limitations, and clinical translation. Ultrasound energy attenuation through the skull, particularly for deep brain tumors, limits effective energy delivery. Additionally, the lack of efficient real-time monitoring technologies to assess BBB opening extent, range, and drug delivery efficacy [173] poses challenges. In clinical trials, variations in skull thickness, brain tumor location, and BBB characteristics among patients may lead to inconsistent MB-FUS effects [196]. Computational design of tightly fitting helmet frames and skull-conformal phased arrays for ultrasound-guided transcranial FUS therapy can improve BBB opening efficiency [203]. However, MRI's limited spatial resolution is not optimal for monitoring BBB disruption and individual blood vessels [204]. Combining MR-guided FUS [205,206], PET/CT guidance [207], and neuronavigation can achieve precise FUS control and real-time navigation. PAI [180–183] or ultrasound imaging [174] can assess BBB opening extent and drug delivery efficacy in real time, optimizing personalized treatment plans. Imaging-guided strategies may enhance precise tumor visualization and minimize residual margins in GBM, reducing postoperative recurrence and prolonging survival [184]. Although MRI can monitor FUS-induced biological effects, its long imaging time, high cost, and lack of portability limit its practical application. Therefore, developing high-resolution, real-time, and portable imaging monitoring technologies is urgently needed.

Current clinical trials are small-scale and mostly in early phases (I/II), lacking large-scale, multicenter phase III trial data to validate safety and efficacy. Optimizing ultrasound parameters, developing novel microbubbles and nanoparticles, combining multimodal imaging, and integrating AI technology can drive large-scale clinical trials, comprehensively assessing the safety and efficacy of MB-FUS- mediated BBB opening and promoting its widespread clinical application. Future research should focus on personalized treatment, novel material development, and multidisciplinary collaboration to further advance MB-FUS technology in brain tumor therapy.

10. Conclusion

Curing brain tumors remains a significant challenge. Chemotherapy can improve brain tumor patient prognosis to some extent, and brain tumor immunotherapy is a current research hotspot. However, the BBB, BTB, and CSF remain major obstacles to chemotherapy. MB-FUS can safely open the BBB, promoting drug entry and enhancing brain tumor treatment. The most extensively studied application is enhancing chemotherapy efficacy, but MB-FUS also enhances radiotherapy, gene delivery, and immunotherapy. Combining SDT with MB-FUS shows great promise. To date, ultrasound-responsive nanomaterials for brain tumor diagnosis and treatment are rapidly developing, and further advancements in materials and technologies will provide more effective treatment strategies for brain tumors.

CRediT authorship contribution statement

Zhiguang Chen: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Liang Sang:** Conceptualization. **Zhai Qixi:** Investigation. **Xiang Li:** Writing – review & editing. **Yanjun Liu:** Writing – review & editing. **ZhiQun Bai:** Writing – review & editing, Methodology.

Ethics approval

Not applicable.

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Declaration of competing interest

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

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Abbreviation

CNS	Central nervous system
ASIR	Age-standardized incidence rate
AAAIR	Average annual age-adjusted incidence rate
GBM	Glioblastoma
BBB	Blood-brain barrier
CSF	Blood-cerebrospinal fluid barrier
BTB	Blood-tumor barrier
MRI	Magnetic resonance imaging
SPIO	Superparamagnetic iron oxide
RMT	Receptor-mediated transcytosis
CMT	carrier-mediated transport
EPR	Enhanced permeability and retention
TMZ	Temozolomide
FUS	Focused ultrasound
MBs	Microbubbles
P-gp	P-glycoprotein
BCRP	breast cancer resistance protein
EB	Evans blue
MI	Mechanical index
PNP	Peak negative pressure
RaSP	Rapid short-pulse
HMONs	hollow mesoporous organosilica nanoparticles
MRgFUS	MR-guided FUS
NPs	Nanoparticles
TAMs	Tumor-associated macrophages
TME	Tumor microenvironment
CAMs	CNS-associated macrophages
ROS	Reactive oxygen species
ppIX	Protoporphyrin IX
HMME	Hematoporphyrin monomethyl ether
SPDT	Sono-piezo dynamic therapy
PDT	Photodynamic therapy
DOX	Doxorubicin
PET	Positron emission tomography
CEUS:	Contrast-enhanced ultrasound
GV	Gas vesicle
fUS:	functional ultrasound imaging
PAI	Photoacoustic imaging
NIR-II	Near-infrared window
AIE	Aggregation-induced emission
ICG	Indocyanine green
PTT	Photothermal therapy
ICD	Immunogenic cell death

Data availability

Data will be made available on request.

References

[1] GBD 2016 Brain and Other CNS Cancer Collaborators, Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 18 (4) (2019) 376–393, https://doi.org/10.1016/S1474-4422(18)30468-X.

[2] X. Liu, L.C. Cheng, T.Y. Gao, J. Luo, C. Zhang, The burden of brain and central nervous system cancers in Asia from 1990 to 2019 and its predicted level in the next twenty-five years : burden and prediction model of CNS cancers in Asia, BMC Public Health 23 (1) (2023) 2522, https://doi.org/10.1186/s12889-023-17467-w.

[3] L.M. DeAngelis, Global consequences of malignant CNS tumours: a call to action, Lancet Neurol. 18 (4) (2019) 324–325, https://doi.org/10.1016/S1474-4422(19)30083-3.

[4] Q.T. Ostrom, G. Cioffi, H. Gittleman, N. Patil, K. Waite, C. Kruchko, J. S. Barnholtz-Sloan, CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016, Neuro Oncol. 21 (Suppl 5) (2019) v1–v100, https://doi.org/10.1093/neuonc/noz150.

[5] A. Hamad, G.M. Yusubalieva, V.P. Baklaushev, P.M. Chumakov, A.V. Lipatova, Recent developments in glioblastoma therapy: oncolytic viruses and emerging future strategies, Viruses 15 (2) (2023) 547, https://doi.org/10.3390/v15020547.

[6] I. Noorani, P.S. Mischel, C. Swanton, Leveraging extrachromosomal DNA to fine-tune trials of targeted therapy for glioblastoma: opportunities and challenges, Nat. Rev. Clin. Oncol. 19 (11) (2022) 733–743, https://doi.org/10.1038/s41571-022-00679-1.

[7] M. Petković, M. Henis, O. Heese, A. Relógio, Chronotherapy in Glioblastoma: state of the art and future perspectives, EBioMedicine 89 (2023) 104470, https://doi.org/10.1016/j.ebiom.2023.104470.

[8] Z. Xiong, I. Raphael, M. Olin, H. Okada, X. Li, G. Kohanbash, Glioblastoma vaccines: past, present, and opportunities, EBioMedicine 100 (2024) 104963, https://doi.org/10.1016/j.ebiom.2023.104963.

[9] A. Omuro, L.M. DeAngelis, Glioblastoma and other malignant gliomas: a clinical review, JAMA 310 (17) (2013) 1842–1850, https://doi.org/10.1001/jama.2013.280319.

[10] A. Degl'Innocenti, N. di Leo, G. Ciofani, Genetic hallmarks and heterogeneity of glioblastoma in the single-cell omics era, Adv. Ther. 3 (1) (2020) 1900152, https://doi.org/10.1002/adtp.201900152.

[11] C. Abbruzzese, S. Matteoni, M. Signore, L. Cardone, K. Nath, J.D. Glickson, M. G. Paggi, Drug repurposing for the treatment of glioblastoma multiforme, J. Exp. Clin. Cancer Res. 36 (1) (2017) 169, https://doi.org/10.1186/s13046-017-0642-x.

[12] GBD 2021 Diseases and Injuries Collaborators, Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021, Lancet 403 (10440) (2024) 2133–2161, https://doi.org/10.1016/S0140-6736(24)00757-8.

[13] Y. Cheng, R.A. Morshed, B. Auffinger, A.L. Tobias, M.S. Lesniak, Multifunctional nanoparticles for brain tumor imaging and therapy, Adv. Drug Deliv. Rev. 66 (2014) 42–57, https://doi.org/10.1016/j.addr.2013.09.006.
[14] J.T. Henderson, M. Piquette-Miller, Blood-brain barrier: an impediment to neuropharmaceuticals, Clin. Pharmacol. Ther. 97 (4) (2015) 308–313, https://doi.org/10.1002/cpt.77.
[15] K. Hynynen, Sounding out the blood-brain barrier, N. Engl. J. Med. 390 (1) (2024) 82–85, https://doi.org/10.1056/NEJMe2311358.
[16] C.D. Arvanitis, G.B. Ferraro, R.K. Jain, The blood-brain barrier and blood-tumour barrier in brain tumours and metastases, Nat. Rev. Cancer 20 (1) (2020) 26–41, https://doi.org/10.1038/s41568-019-0205-x.
[17] P. Solár, A. Zamani, L. Kubíčková, P. Dubový, M. Joukal, Choroid plexus and the blood-cerebrospinal fluid barrier in disease, Fluids Barriers CNS 17 (1) (2020) 35, https://doi.org/10.1186/s12987-020-00196-2.
[18] F. Han, J. Gao, G. Lv, T. Liu, Q. Hu, M. Zhu, Z. Du, J. Yang, Z. Yao, X. Fang, D. Ni, J. Zhang, Magnetic resonance imaging with upconversion nanoprobes capable of crossing the blood-cerebrospinal fluid barrier, J. Nanobiotechnol. 22 (1) (2024) 43, https://doi.org/10.1186/s12951-024-02301-1.
[19] X. Chen, A. Momin, S. Wanggou, X. Wang, H.K. Min, W. Dou, Z. Gong, J. Chan, W. Dong, J.J. Fan, Y. Xiong, K. Talipova, H. Zhao, Y.X. Chen, K. Veerasammy, A. Fekete, S.A. Kumar, H. Liu, Q. Yang, J.E. Son, Z. Dou, M. Hu, P. Pardis, K. Juraschka, L.K. Donovan, J. Zhang, V. Ramaswamy, H.J. Selvadurai, P. B. Dirks, M.D. Taylor, L.Y. Wang, C.C. Hui, R. Abzalimov, Y. He, Y. Sun, X. Li, X. Huang, Mechanosensitive brain tumor cells construct blood-tumor barrier to mask chemosensitivity, Neuron 111 (1) (2023) 30–48.e14, https://doi.org/10.1016/j.neuron.2022.10.007.
[20] S. Xu, G. Zhang, J. Zhang, W. Liu, Y. Wang, X. Fu, Advances in brain tumor therapy based on the magnetic nanoparticles, Int. J. Nanomed. 18 (2023) 7803–7823, https://doi.org/10.2147/IJN.S444319.
[21] J. Xie, S. Lee, X. Chen, Nanoparticle-based theranostic agents, Adv. Drug Deliv. Rev. 62 (11) (2010) 1064–1079, https://doi.org/10.1016/j.addr.2010.07.009.
[22] X. Gao, Q. Yue, Z. Liu, M. Ke, X. Zhou, S. Li, J. Zhang, R. Zhang, L. Chen, Y. Mao, C. Li, Guiding brain-tumor surgery via blood-brain-barrier-permeable gold nanoprobes with acid-triggered MRI/SERRS signals, Adv. Mater. 29 (21) (2017), https://doi.org/10.1002/adma.201603917.
[23] C.H. Fan, C.Y. Ting, H.J. Lin, C.H. Wang, H.L. Liu, T.C. Yen, C.K. Yeh, SPIO-conjugated, doxorubicin-loaded microbubbles for concurrent MRI and focused-ultrasound enhanced brain-tumor drug delivery, Biomaterials 34 (14) (2013) 3706–3715, https://doi.org/10.1016/j.biomaterials.2013.01.099.
[24] H.K. Kim, G.H. Lee, Y. Chang, Gadolinium as an MRI contrast agent, Future Med. Chem. 10 (6) (2018) 639–661, https://doi.org/10.4155/fmc-2017-0215.
[25] R.E. Kalb, T.N. Helm, H. Sperry, C. Thakral, J.L. Abraham, E. Kanal, Gadolinium-induced nephrogenic systemic fibrosis in a patient with an acute and transient kidney injury, Br. J. Dermatol. 158 (3) (2008) 607–610, https://doi.org/10.1111/j.1365-2133.2007.08369.x.
[26] N. Güvener, L. Appold, F. de Lorenzi, S.K. Golombek, L.Y. Rizzo, T. Lammers, F. Kiessling, Recent advances in ultrasound-based diagnosis and therapy with micro- and nanometer-sized formulations, Methods 130 (2017) 4–13, https://doi.org/10.1016/j.ymeth.2017.05.018.
[27] F. Qu, P. Wang, K. Zhang, Y. Shi, Y. Li, C. Li, J. Lu, Q. Liu, X. Wang, Manipulation of Mitophagy by "All-in-One" nanosensitizer augments sonodynamic glioma therapy, Autophagy 16 (8) (2020) 1413–1435, https://doi.org/10.1080/15548627.2019.1687210.
[28] H. Chen, S. Zhang, Q. Fang, H. He, J. Ren, D. Sun, J. Lai, A. Ma, Z. Chen, L. Liu, R. Liang, L. Cai, Biomimetic nanosonosensitizers combined with noninvasive ultrasound actuation to reverse drug resistance and sonodynamic-enhanced chemotherapy against orthotopic glioblastoma, ACS Nano 17 (1) (2023) 421–436, https://doi.org/10.1021/acsnano.2c08861.
[29] Floc'h J. Le, H.D. Lu, T.L. Lim, C. Démoré, R.K. Prud'homme, K. Hynynen, F. S. Foster, Transcranial photoacoustic detection of blood-brain barrier disruption following focused ultrasound-mediated nanoparticle delivery, Mol. Imag. Biol. 22 (2) (2020) 324–334, https://doi.org/10.1007/s11307-019-01397-4.
[30] Y.C. Chen, C.F. Chiang, S.K. Wu, L.F. Chen, W.Y. Hsieh, W.L. Lin, Targeting microbubbles-carrying TGFβ1 inhibitor combined with ultrasound sonication induce BBB/BTB disruption to enhance nanomedicine treatment for brain tumors, J. Contr. Release 211 (2015) 53–62, https://doi.org/10.1016/j.jconrel.2015.05.288.
[31] Z. Zhao, A.R. Nelson, C. Betsholtz, B.V. Zlokovic, Establishment and dysfunction of the blood-brain barrier, Cell 163 (5) (2015) 1064–1078, https://doi.org/10.1016/j.cell.2015.10.067.
[32] J. Xie, Z. Shen, Y. Anraku, K. Kataoka, X. Chen, Nanomaterial-based blood-brain-barrier (BBB) crossing strategies, Biomaterials 224 (2019) 119491, https://doi.org/10.1016/j.biomaterials.2019.119491.
[33] A.F. Eichler, E. Chung, D.P. Kodack, J.S. Loeffler, D. Fukumura, R.K. Jain, The biology of brain metastases-translation to new therapies, Nat. Rev. Clin. Oncol. 8 (6) (2011) 344–356, https://doi.org/10.1038/nrclinonc.2011.58.
[34] D. Knowland, A. Arac, K.J. Sekiguchi, M. Hsu, S.E. Lutz, J. Perrino, G. K. Steinberg, B.A. Barres, A. Nimmerjahn, D. Agalliu, Stepwise recruitment of transcellular and paracellular pathways underlies blood-brain barrier breakdown in stroke, Neuron 82 (3) (2014) 603–617, https://doi.org/10.1016/j.neuron.2014.03.003.
[35] A. Ben-Zvi, B. Lacoste, E. Kur, B.J. Andreone, Y. Mayshar, H. Yan, C. Gu, Mfsd2a is critical for the formation and function of the blood-brain barrier, Nature 509 (7501) (2014) 507–511, https://doi.org/10.1038/nature13324.
[36] W.M. Pardridge, Targeted delivery of protein and gene medicines through the blood-brain barrier, Clin. Pharmacol. Ther. 97 (4) (2015) 347–361, https://doi.org/10.1002/cpt.18.
[37] R. Pandit, L. Chen, J. Götz, The blood-brain barrier: physiology and strategies for drug delivery, Adv. Drug Deliv. Rev. 165–166 (2020) 1–14, https://doi.org/10.1016/j.addr.2019.11.009.
[38] W.J. Geldenhuys, A.S. Mohammad, C.E. Adkins, P.R. Lockman, Molecular determinants of blood-brain barrier permeation, Ther. Deliv. 6 (8) (2015) 961–971, https://doi.org/10.4155/tde.15.32.
[39] W.M. Pardridge, Blood-brain barrier endogenous transporters as therapeutic targets: a new model for small molecule CNS drug discovery, Expert Opin. Ther. Targets 19 (8) (2015) 1059–1072, https://doi.org/10.1517/14728222.2015.1042364.
[40] L. Han, C. Jiang, Evolution of blood-brain barrier in brain diseases and related systemic nanoscale brain-targeting drug delivery strategies, Acta Pharm. Sin. B 11 (8) (2021) 2306–2325, https://doi.org/10.1016/j.apsb.2020.11.023.
[41] N.J. Abbott, L. Rönnbäck, E. Hansson, Astrocyte-endothelial interactions at the blood-brain barrier, Nat. Rev. Neurosci. 7 (1) (2006) 41–53, https://doi.org/10.1038/nrn1824.
[42] Y. Chen, L. Liu, Modern methods for delivery of drugs across the blood-brain barrier, Adv. Drug Deliv. Rev. 64 (7) (2012) 640–665, https://doi.org/10.1016/j.addr.2011.11.010.
[43] M.D. Sweeney, A.P. Sagare, B.V. Zlokovic, Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders, Nat. Rev. Neurol. 14 (3) (2018) 133–150, https://doi.org/10.1038/nrneurol.2017.188.
[44] L.P. Wu, D. Ahmadvand, J. Su, A. Hall, X. Tan, Z.S. Farhangrazi, S.M. Moghimi, Crossing the blood-brain-barrier with nanoligand drug carriers self-assembled from a phage display peptide, Nat. Commun. 10 (1) (2019) 4635, https://doi.org/10.1038/s41467-019-12554-2.
[45] T. Chen, C. Li, Y. Li, X. Yi, R. Wang, S.M. Lee, Y. Zheng, Small-Sized mPEG-PLGA nanoparticles of schisantherin A with sustained release for enhanced brain uptake and anti-parkinsonian activity, ACS Appl. Mater. Interfaces 9 (11) (2017) 9516–9527, https://doi.org/10.1021/acsami.7b01171.
[46] H. Maeda, J. Wu, T. Sawa, Y. Matsumura, K. Hori, Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review, J. Contr. Release 65 (1–2) (2000) 271–284, https://doi.org/10.1016/s0168-3659(99)00248-5.
[47] J.D. Meyers, T. Doane, C. Burda, J.P. Basilion, Nanoparticles for imaging and treating brain cancer, Nanomedicine 8 (1) (2013) 123–143, https://doi.org/10.2217/nnm.12.185.
[48] Y. Cheng, R.A. Morshed, B. Auffinger, A.L. Tobias, M.S. Lesniak, Multifunctional nanoparticles for brain tumor imaging and therapy, Adv. Drug Deliv. Rev. 66 (2014) 42–57, https://doi.org/10.1016/j.addr.2013.09.006.
[49] K.D. Macklin, A.D. Maus, E.F. Pereira, E.X. Albuquerque, B.M. Conti-Fine, Human vascular endothelial cells express functional nicotinic acetylcholine receptors, J. Pharmacol. Exp. Therapeut. 287 (1) (1998) 435–439.
[50] R. Pasqualini, E. Koivunen, R. Kain, J. Lahdenranta, M. Sakamoto, A. Stryhn, R. A. Ashmun, L.H. Shapiro, W. Arap, E. Ruoslahti, Aminopeptidase N is a receptor for tumor-homing peptides and a target for inhibiting angiogenesis, Cancer Res. 60 (3) (2000) 722–727.
[51] S. Reddy, K. Tatiparti, S. Sau, A.K. Iyer, Recent advances in nano delivery systems for blood-brain barrier (BBB) penetration and targeting of brain tumors, Drug Discov. Today 26 (8) (2021) 1944–1952, https://doi.org/10.1016/j.drudis.2021.04.008.
[52] S. Hadidchi, W. Surento, A. Lerner, C.J. Liu, W.N. Gibbs, P.E. Kim, M.S. Shiroishi, Headache and brain tumor, Neuroimaging Clin. 29 (2) (2019) 291–300, https://doi.org/10.1016/j.nic.2019.01.008.
[53] L. Vercueil, Brain tumor epilepsy: a reappraisal and six remaining issues to be debated, Rev. Neurol. (Paris) 167 (10) (2011) 751–761, https://doi.org/10.1016/j.neurol.2011.08.007.
[54] O. van Tellingen, B. Yetkin-Arik, M.C. de Gooijer, P. Wesseling, T. Wurdinger, H. E. de Vries, Overcoming the blood-brain tumor barrier for effective glioblastoma treatment, Drug Resist. Updates 19 (2015) 1–12, https://doi.org/10.1016/j.drup.2015.02.002.
[55] C. Sun, Y. Ding, L. Zhou, D. Shi, L. Sun, T.J. Webster, Y. Shen, Noninvasive nanoparticle strategies for brain tumor targeting, Nanomedicine 13 (8) (2017) 2605–2621, https://doi.org/10.1016/j.nano.2017.07.009.
[56] Y.H. Tsou, X.Q. Zhang, H. Zhu, S. Syed, X. Xu, Drug delivery to the brain across the blood-brain barrier using nanomaterials, Small 13 (43) (2017), https://doi.org/10.1002/smll.201701921.
[57] L. Jena, E. McErlean, H. McCarthy, Delivery across the blood-brain barrier: nanomedicine for glioblastoma multiforme, Drug Deliv Transl Res 10 (2) (2020) 304–318, https://doi.org/10.1007/s13346-019-00679-2.
[58] J. Skog, T. Würdinger, S. van Rijn, D.H. Meijer, L. Gainche, M. Sena-Esteves, WT Jr Curry, B.S. Carter, A.M. Krichevsky, X.O. Breakefield, Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers, Nat. Cell Biol. 10 (12) (2008) 1470–1476, https://doi.org/10.1038/ncb1800.
[59] F.U. Rehman, Y. Liu, M. Zheng, B. Shi, Exosomes based strategies for brain drug delivery, Biomaterials 293 (2023) 121949, https://doi.org/10.1016/j.biomaterials.2022.121949.
[60] J. Wang, W. Tang, M. Yang, Y. Yin, H. Li, F. Hu, L. Tang, X. Ma, Y. Zhang, Y. Wang, Inflammatory tumor microenvironment responsive neutrophil exosomes-based drug delivery system for targeted glioma therapy, Biomaterials 273 (2021) 120784, https://doi.org/10.1016/j.biomaterials.2021.120784.
[61] Q. Zhan, K. Yi, X. Cui, X. Li, S. Yang, Q. Wang, C. Fang, Y. Tan, L. Li, C. Xu, X. Yuan, C. Kang, Blood exosomes-based targeted delivery of cPLA2 siRNA and

metformin to modulate glioblastoma energy metabolism for tailoring personalized therapy, Neuro Oncol. 24 (11) (2022) 1871–1883, https://doi.org/10.1093/neuonc/noac071.
[62] D. Rufino-Ramos, P.R. Albuquerque, V. Carmona, R. Perfeito, R.J. Nobre, L. Pereira de Almeida, Extracellular vesicles: novel promising delivery systems for therapy of brain diseases, J. Contr. Release 262 (2017) 247–258, https://doi.org/10.1016/j.jconrel.2017.07.001.
[63] W. Hao, Y. Cui, Y. Fan, M. Chen, G. Yang, Y. Wang, M. Yang, Z. Li, W. Gong, Y. Yang, C. Gao, Hybrid membrane-coated nanosuspensions for multi-modal anti-glioma therapy via drug and antigen delivery, J. Nanobiotechnol. 19 (1) (2021) 378, https://doi.org/10.1186/s12951-021-01110-0.
[64] W. Niu, Q. Xiao, X. Wang, J. Zhu, J. Li, X. Liang, Y. Peng, C. Wu, R. Lu, Y. Pan, J. Luo, X. Zhong, H. He, Z. Rong, J.B. Fan, Y. Wang, A biomimetic drug delivery system by integrating grapefruit extracellular vesicles and doxorubicin-loaded heparin-based nanoparticles for glioma therapy, Nano Lett. 21 (3) (2021) 1484–1492, https://doi.org/10.1021/acs.nanolett.0c04753.
[65] Z. Wang, M. Zhang, S. Chi, M. Zhu, C. Wang, Z. Liu, Brain tumor cell membrane-coated lanthanide-doped nanoparticles for NIR-IIb luminescence imaging and surgical navigation of glioma, Adv. Healthcare Mater. 11 (16) (2022) e2200521, https://doi.org/10.1002/adhm.202200521.
[66] S. Strickland, M. Jorns, L. Fourroux, L. Heyd, D. Pappas, Cancer cell targeting via selective transferrin receptor labeling using protein-derived carbon dots, ACS Omega 9 (2) (2024) 2707–2718, https://doi.org/10.1021/acsomega.3c07744.
[67] Y.J. Kang, E.G. Cutler, H. Cho, Therapeutic nanoplatforms and delivery strategies for neurological disorders, Nano Converg 5 (1) (2018) 35, https://doi.org/10.1186/s40580-018-0168-8.
[68] F. Xie, N. Yao, Y. Qin, Q. Zhang, H. Chen, M. Yuan, J. Tang, X. Li, W. Fan, Q. Zhang, Y. Wu, L. Hai, Q. He, Investigation of glucose-modified liposomes using polyethylene glycols with different chain lengths as the linkers for brain targeting, Int. J. Nanomed. 7 (2012) 163–175, https://doi.org/10.2147/IJN.S23771.
[69] Z. Qiu, Z. Yu, T. Xu, L. Wang, N. Meng, H. Jin, B. Xu, Novel nano-drug delivery system for brain tumor treatment, Cells 11 (23) (2022) 3761, https://doi.org/10.3390/cells11233761.
[70] Z. Pang, H. Gao, J. Chen, S. Shen, B. Zhang, J. Ren, L. Guo, Y. Qian, X. Jiang, H. Mei, Intracellular delivery mechanism and brain delivery kinetics of biodegradable cationic bovine serum albumin-conjugated polymersomes, Int. J. Nanomed. 7 (2012) 3421–3432, https://doi.org/10.2147/IJN.S32514.
[71] Ö. Şen, M. Emanet, M. Mazzuferi, M. Bartolucci, F. Catalano, M. Prato, S. Moscato, A. Marino, D. De Pasquale, G. Pugliese, F. Bonaccorso, V. Pellegrini, A.E.D.R. Castillo, A. Petretto, G. Ciofani, Microglia polarization and antiglioma effects fostered by dual cell membrane-coated doxorubicin-loaded hexagonal boron nitride nanoflakes, ACS Appl. Mater. Interfaces 15 (50) (2023) 58260–58273, https://doi.org/10.1021/acsami.3c17097.
[72] D. De Pasquale, A. Marino, C. Tapeinos, C. Pucci, S. Rocchiccioli, E. Michelucci, F. Finamore, L. McDonnell, A. Scarpellini, S. Lauciello, M. Prato, A. Larrañaga, F. Drago, G. Ciofani, Homotypic targeting and drug delivery in glioblastoma cells through cell membrane-coated boron nitride nanotubes, Mater. Des. 192 (2020) 108742, https://doi.org/10.1016/j.matdes.2020.108742.
[73] E.R. de Oliveira Junior, T.L. Nascimento, M.A. Salomão, A.C.G. da Silva, M. C. Valadares, E.M. Lima, Increased nose-to-brain delivery of melatonin mediated by polycaprolactone nanoparticles for the treatment of glioblastoma, Pharm. Res. 36 (9) (2019) 131, https://doi.org/10.1007/s11095-019-2662-z.
[74] N.I. Vykhodtseva, K. Hynynen, C. Damianou, Histologic effects of high intensity pulsed ultrasound exposure with subharmonic emission in rabbit brain in vivo, Ultrasound Med. Biol. 21 (7) (1995) 969–979, https://doi.org/10.1016/0301-5629(95)00038-s.
[75] A. Burgess, K. Shah, O. Hough, K. Hynynen, Focused ultrasound-mediated drug delivery through the blood-brain barrier, Expert Rev. Neurother. 15 (5) (2015) 477–491, https://doi.org/10.1586/14737175.2015.1028369.
[76] K. Hynynen, N. McDannold, N. Vykhodtseva, F.A. Jolesz, Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits, Radiology 220 (3) (2001) 640–646, https://doi.org/10.1148/radiol.2202001804.
[77] P. Dayton, A. Klibanov, G. Brandenburger, K. Ferrara, Acoustic radiation force in vivo: a mechanism to assist targeting of microbubbles, Ultrasound Med. Biol. 25 (8) (1999) 1195–1201, https://doi.org/10.1016/s0301-5629(99)00062-9.
[78] D.L. Miller, N.B. Smith, M.R. Bailey, G.J. Czarnota, K. Hynynen, I.R. Makin, Bioeffects Committee of the American Institute of Ultrasound in Medicine, Overview of therapeutic ultrasound applications and safety considerations, J. Ultrasound Med. 31 (4) (2012) 623–634, https://doi.org/10.7863/jum.2012.31.4.623.
[79] N. Hosseinkhah, K. Hynynen, A three-dimensional model of an ultrasound contrast agent gas bubble and its mechanical effects on microvessels, Phys. Med. Biol. 57 (3) (2012) 785–808, https://doi.org/10.1088/0031-9155/57/3/785.
[80] L. Krizanac-Bengez, M.R. Mayberg, D. Janigro, The cerebral vasculature as a therapeutic target for neurological disorders and the role of shear stress in vascular homeostatis and pathophysiology, Neurol. Res. 26 (8) (2004) 846–853, https://doi.org/10.1179/016164104X3789.
[81] W.L. Nyborg, Biological effects of ultrasound: development of safety guidelines. Part II: general review, Ultrasound Med. Biol. 27 (3) (2001) 301–333, https://doi.org/10.1016/s0301-5629(00)00333-1.
[82] O. Traub, T. Ishida, M. Ishida, J.C. Tupper, B.C. Berk, Shear stress-mediated extracellular signal-regulated kinase activation is regulated by sodium in endothelial cells. Potential role for a voltage-dependent sodium channel, J. Biol. Chem. 274 (29) (1999) 20144–20150, https://doi.org/10.1074/jbc.274.29.20144.
[83] H.L. Liu, C.H. Fan, C.Y. Ting, C.K. Yeh, Combining microbubbles and ultrasound for drug delivery to brain tumors: current progress and overview, Theranostics 4 (4) (2014) 432–444, https://doi.org/10.7150/thno.8074.
[84] J.J. Choi, J.A. Feshitan, B. Baseri, S. Wang, Y.S. Tung, M.A. Borden, E. E. Konofagou, Microbubble-size dependence of focused ultrasound-induced blood-brain barrier opening in mice in vivo, IEEE Trans. Biomed. Eng. 57 (1) (2010) 145–154, https://doi.org/10.1109/TBME.2009.2034533.
[85] N. Sheikov, N. McDannold, N. Vykhodtseva, F. Jolesz, K. Hynynen, Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles, Ultrasound Med. Biol. 30 (7) (2004) 979–989, https://doi.org/10.1016/j.ultrasmedbio.2004.04.010.
[86] X. Shang, P. Wang, Y. Liu, Z. Zhang, Y. Xue, Mechanism of low-frequency ultrasound in opening blood-tumor barrier by tight junction, J. Mol. Neurosci. 43 (3) (2011) 364–369, https://doi.org/10.1007/s12031-010-9451-9.
[87] S. Jalali, Y. Huang, D.J. Dumont, K. Hynynen, Focused ultrasound-mediated bbb disruption is associated with an increase in activation of AKT: experimental study in rats, BMC Neurol. 10 (2010) 114, https://doi.org/10.1186/1471-2377-10-114.
[88] H. Cho, H.Y. Lee, M. Han, J.R. Choi, S. Ahn, T. Lee, Y. Chang, J. Park, Localized down-regulation of P-glycoprotein by focused ultrasound and microbubbles induced blood-brain barrier disruption in rat brain, Sci. Rep. 6 (2016) 31201, https://doi.org/10.1038/srep31201.
[89] A. Conti, F. Geffroy, H.A.S. Kamimura, A. Novell, N. Tournier, S. Mériaux, B. Larrat, Regulation of P-glycoprotein and breast cancer resistance protein expression induced by focused ultrasound-mediated blood-brain barrier disruption: a pilot study, Int. J. Mol. Sci. 23 (24) (2022) 15488, https://doi.org/10.3390/ijms232415488.
[90] N. Sheikov, N. McDannold, F. Jolesz, Y.Z. Zhang, K. Tam, K. Hynynen, Brain arterioles show more active vesicular transport of blood-borne tracer molecules than capillaries and venules after focused ultrasound-evoked opening of the blood-brain barrier, Ultrasound Med. Biol. 32 (9) (2006) 1399–1409, https://doi.org/10.1016/j.ultrasmedbio.2006.05.015.
[91] D. McMahon, C. Poon, K. Hynynen, Evaluating the safety profile of focused ultrasound and microbubble-mediated treatments to increase blood-brain barrier permeability, Expet Opin. Drug Deliv. 16 (2) (2019) 129–142, https://doi.org/10.1080/17425247.2019.1567490.
[92] C. Poon, D. McMahon, K. Hynynen, Noninvasive and targeted delivery of therapeutics to the brain using focused ultrasound, Neuropharmacology 120 (2017) 20–37, https://doi.org/10.1016/j.neuropharm.2016.02.014.
[93] P.C. Chu, W.Y. Chai, C.H. Tsai, S.T. Kang, C.K. Yeh, H.L. Liu, Focused ultrasound-induced blood-brain barrier opening: association with mechanical index and cavitation index analyzed by dynamic contrast-enhanced magnetic-resonance imaging, Sci. Rep. 6 (2016) 33264, https://doi.org/10.1038/srep33264.
[94] S.K. Wu, P.C. Chu, W.Y. Chai, S.T. Kang, C.H. Tsai, C.H. Fan, C.K. Yeh, H.L. Liu, Characterization of different microbubbles in assisting focused ultrasound-induced blood-brain barrier opening, Sci. Rep. 7 (2017) 46689, https://doi.org/10.1038/srep46689.
[95] D. McMahon, A. Lassus, E. Gaud, V. Jeannot, K. Hynynen, Microbubble formulation influences inflammatory response to focused ultrasound exposure in the brain, Sci. Rep. 10 (1) (2020) 21534, https://doi.org/10.1038/s41598-020-78657-9.
[96] D. McMahon, L. Deng, K. Hynynen, Comparing rapid short-pulse to tone burst sonication sequences for focused ultrasound and microbubble-mediated blood-brain barrier permeability enhancement, J. Contr. Release 329 (2021) 696–705, https://doi.org/10.1016/j.jconrel.2020.10.004.
[97] N. McDannold, Y. Zhang, N. Vykhodtseva, The effects of oxygen on ultrasound-induced blood-brain barrier disruption in mice, Ultrasound Med. Biol. 43 (2) (2017) 469–475, https://doi.org/10.1016/j.ultrasmedbio.2016.09.019.
[98] G. Samiotaki, F. Vlachos, Y.S. Tung, E.E. Konofagou, A quantitative pressure and microbubble-size dependence study of focused ultrasound-induced blood-brain barrier opening reversibility in vivo using MRI, Magn. Reson. Med. 67 (3) (2012) 769–777, https://doi.org/10.1002/mrm.23063.
[99] D.E. Goertz, N. de Jong, A.F. van der Steen, Attenuation and size distribution measurements of Definity and manipulated Definity populations, Ultrasound Med. Biol. 33 (9) (2007) 1376–1388, https://doi.org/10.1016/j.ultrasmedbio.2007.03.009.
[100] K.H. Song, A.C. Fan, J.J. Hinkle, J. Newman, M.A. Borden, B.K. Harvey, Microbubble gas volume: a unifying dose parameter in blood-brain barrier opening by focused ultrasound, Theranostics 7 (1) (2017) 144–152, https://doi.org/10.7150/thno.15987.
[101] J. Shin, C. Kong, J.S. Cho, J. Lee, C.S. Koh, M.S. Yoon, Y.C. Na, W.S. Chang, J. W. Chang, Focused ultrasound-mediated noninvasive blood-brain barrier modulation: preclinical examination of efficacy and safety in various sonication parameters, Neurosurg. Focus 44 (2) (2018) E15, https://doi.org/10.3171/2017.11.FOCUS17627.
[102] O.L. Chinot, W. Wick, W. Mason, R. Henriksson, F. Saran, R. Nishikawa, A. F. Carpentier, K. Hoang-Xuan, P. Kavan, D. Cernea, A.A. Brandes, M. Hilton, L. Abrey, T. Cloughesy, Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (8) (2014) 709–722, https://doi.org/10.1056/NEJMoa1308345.
[103] H.L. Liu, C.Y. Huang, J.Y. Chen, H.Y. Wang, P.Y. Chen, K.C. Wei, Pharmacodynamic and therapeutic investigation of focused ultrasound-induced blood-brain barrier opening for enhanced temozolomide delivery in glioma treatment, PLoS One 9 (12) (2014) e114311, https://doi.org/10.1371/journal.pone.0114311.
[104] K. Beccaria, M. Canney, L. Goldwirt, C. Fernandez, J. Piquet, M.C. Perier, C. Lafon, J.Y. Chapelon, A. Carpentier, Ultrasound-induced opening of the blood-

brain barrier to enhance temozolomide and irinotecan delivery: an experimental study in rabbits, J. Neurosurg. 124 (6) (2016) 1602–1610, https://doi.org/10.3171/2015.4.JNS142893.
[105] M. Wu, W. Chen, Y. Chen, H. Zhang, C. Liu, Z. Deng, Z. Sheng, J. Chen, X. Liu, F. Yan, H. Zheng, Focused ultrasound-augmented delivery of biodegradable multifunctional nanoplatforms for imaging-guided brain tumor treatment, Adv. Sci. 5 (4) (2018) 1700474, https://doi.org/10.1002/advs.201700474.
[106] M. Kinoshita, N. McDannold, F.A. Jolesz, K. Hynynen, Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption, Proc. Natl. Acad. Sci. USA. 103 (31) (2006) 11719–11723, https://doi.org/10.1073/pnas.0604318103.
[107] C.D. Arvanitis, V. Askoxylakis, Y. Guo, M. Datta, J. Kloepper, G.B. Ferraro, M. O. Bernabeu, D. Fukumura, N. McDannold, R.K. Jain, Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood-tumor barrier disruption, Proc. Natl. Acad. Sci. USA. 115 (37) (2018) E8717–E8726, https://doi.org/10.1073/pnas.1807105115.
[108] A. Bunevicius, N.J. McDannold, A.J. Golby, Focused ultrasound strategies for brain tumor therapy, Oper Neurosurg (Hagerstown). 19 (1) (2020) 9–18, https://doi.org/10.1093/ons/opz374.
[109] J. Mei, Y. Cheng, Y. Song, Y. Yang, F. Wang, Y. Liu, Z. Wang, Experimental study on targeted methotrexate delivery to the rabbit brain via magnetic resonance imaging-guided focused ultrasound, J. Ultrasound Med. 28 (7) (2009) 871–880, https://doi.org/10.7863/jum.2009.28.7.871.
[110] N. McDannold, Y. Zhang, J.G. Supko, C. Power, T. Sun, C. Peng, N. Vykhodtseva, A.J. Golby, D.A. Reardon, Acoustic feedback enables safe and reliable carboplatin delivery across the blood-brain barrier with a clinical focused ultrasound system and improves survival in a rat glioma model, Theranostics 9 (21) (2019) 6284–6299, https://doi.org/10.7150/thno.35892.
[111] T. Mainprize, N. Lipsman, Y. Huang, Y. Meng, A. Bethune, S. Ironside, C. Heyn, R. Alkins, M. Trudeau, A. Sahgal, J. Perry, K. Hynynen, Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: a clinical safety and feasibility study, Sci. Rep. 9 (1) (2019) 321, https://doi.org/10.1038/s41598-018-36340-0.
[112] K. Almeida Lima, I.Y.A. Osawa, M.C.C. Ramalho, I. de Souza, C.B. Guedes, C.H. D. Souza Filho, L.K.S. Monteiro, M.T. Latancia, C.R.R. Rocha, Temozolomide resistance in glioblastoma by NRF2: protecting the evil, Biomedicines 11 (4) (2023) 1081, https://doi.org/10.3390/biomedicines11041081.
[113] S. Wang, C.C. Wu, H. Zhang, M.E. Karakatsani, Y.F. Wang, Y. Han, K. R. Chaudhary, C.S. Wuu, E. Konofagou, S.K. Cheng, Focused ultrasound induced-blood-brain barrier opening in mouse brain receiving radiosurgery dose of radiation enhances local delivery of systemic therapy, Br. J. Radiol. 93 (1109) (2020) 20190214, https://doi.org/10.1259/bjr.20190214.
[114] P.J. White, Y.Z. Zhang, C. Power, N. Vykhodtseva, N. McDannold, Observed effects of whole-brain radiation therapy on focused ultrasound blood-brain barrier disruption, Ultrasound Med. Biol. 46 (8) (2020) 1998–2006, https://doi.org/10.1016/j.ultrasmedbio.2020.04.013.
[115] K.T. Chen, C.Y. Huang, P.C. Pai, W.C. Yang, C.K. Tseng, H.C. Tsai, J.C. Li, C. C. Chuang, P.W. Hsu, C.C. Lee, C.H. Toh, H.L. Liu, K.C. Wei, Focused ultrasound combined with radiotherapy for malignant brain tumor: a preclinical and clinical study, J. Neuro Oncol. 165 (3) (2023) 535–545, https://doi.org/10.1007/s11060-023-04517-x.
[116] J.L. Mergny, D. Sen, DNA quadruple helices in nanotechnology, Chem. Rev. 119 (10) (2019) 6290–6325, https://doi.org/10.1021/acs.chemrev.8b00629.
[117] T. Liedl, Nanotechnology: pathfinder for DNA constructs, Nature 523 (7561) (2015) 412–413, https://doi.org/10.1038/523412a.
[118] Y. Shen, M. Hu, W. Li, Y. Chen, Y. Xu, L. Sun, D. Liu, S. Chen, Y. Gu, Y. Ma, X. Chen, Delivery of DNA octahedra enhanced by focused ultrasound with microbubbles for glioma therapy, J. Contr. Release 350 (2022) 158–174, https://doi.org/10.1016/j.jconrel.2022.08.019.
[119] C.Y. Lin, H.Y. Hsieh, W.G. Pitt, C.Y. Huang, I.C. Tseng, C.K. Yeh, K.C. Wei, H. L. Liu, Focused ultrasound-induced blood-brain barrier opening for non-viral, non-invasive, and targeted gene delivery, J. Contr. Release 212 (2015) 1–9, https://doi.org/10.1016/j.jconrel.2015.06.010.
[120] A.E. Aly, T. Sun, Y. Zhang, Z. Li, M. Kyada, Q. Ma, L. Padegimas, O. Sesenoglu-Laird, M.J. Cooper, N.J. McDannold, B.L. Waszczak, Focused ultrasound enhances transgene expression of intranasal hGDNF DNA nanoparticles in the sonicated brain regions, J. Contr. Release 358 (2023) 498–509, https://doi.org/10.1016/j.jconrel.2023.04.041.
[121] B.P. Mead, P. Mastorakos, J.S. Suk, A.L. Klibanov, J. Hanes, R.J. Price, Targeted gene transfer to the brain via the delivery of brain-penetrating DNA nanoparticles with focused ultrasound, J. Contr. Release 223 (2016) 109–117, https://doi.org/10.1016/j.jconrel.2015.12.034.
[122] G. Zhao, Q. Huang, F. Wang, X. Zhang, J. Hu, Y. Tan, N. Huang, Z. Wang, Z. Wang, Y. Cheng, Targeted shRNA-loaded liposome complex combined with focused ultrasound for blood brain barrier disruption and suppressing glioma growth, Cancer Lett. 418 (2018) 147–158, https://doi.org/10.1016/j.canlet.2018.01.035.
[123] K. Ogawa, N. Kato, M. Yoshida, T. Hiu, T. Matsuo, S. Mizukami, D. Omata, R. Suzuki, K. Maruyama, H. Mukai, S. Kawakami, Focused ultrasound/microbubbles-assisted BBB opening enhances LNP-mediated mRNA delivery to brain, J. Contr. Release 348 (2022) 34–41, https://doi.org/10.1016/j.jconrel.2022.05.042.
[124] C. Kim, M. Lim, G.F. Woodworth, C.D. Arvanitis, The roles of thermal and mechanical stress in focused ultrasound-mediated immunomodulation and immunotherapy for central nervous system tumors, J. Neuro Oncol. 157 (2) (2022) 221–236, https://doi.org/10.1007/s11060-022-03973-1.
[125] T. Balzano, J.A. Pineda-Pardo, N. Esteban-García, M. López-Aguirre, A. Reinares-Sebastián, I. Trigo-Damas, M. Takada, J.A. Obeso, J. Blesa, Temporal dynamics of neurovascular unit changes following blood-brain barrier opening in the putamen of non-human primates, J. Contr. Release 377 (2025) 116–126, https://doi.org/10.1016/j.jconrel.2024.11.019.
[126] H. Chen, D. Koul, Y. Zhang, S.N. Ghobadi, Y. Zhu, Q. Hou, E. Chang, F.G. Habte, R. Paulmurugan, S. Khan, Y. Zheng, M.B. Graeber, I. Herschmann, K.S. Lee, M. Wintermark, Pulsed focused ultrasound alters the proteomic profile of the tumor microenvironment in a syngeneic mouse model of glioblastoma, J. Neuro Oncol. 170 (2) (2024) 347–361, https://doi.org/10.1007/s11060-024-04801-4.
[127] A.R. Kline-Schoder, S. Chintamen, M.J. Willner, M.R. DiBenedetto, R.L. Noel, A. J. Batts, N. Kwon, S. Zacharoulis, C.C. Wu, V. Menon, S.G. Kernie, E.E. Konofagou, Characterization of the responses of brain macrophages to focused ultrasound-mediated blood-brain barrier opening, Nat. Biomed. Eng. 8 (5) (2024) 650–663, https://doi.org/10.1038/s41551-023-01107-0.
[128] A. Sabbagh, K. Beccaria, X. Ling, A. Marisetty, M. Ott, H. Caruso, E. Barton, L. Y. Kong, D. Fang, K. Latha, D.Y. Zhang, J. Wei, J. DeGroot, M.A. Curran, G. Rao, J. Hu, C. Desseaux, G. Bouchoux, M. Canney, A. Carpentier, A.B. Heimberger, Opening of the blood-brain barrier using low-intensity pulsed ultrasound enhances responses to immunotherapy in preclinical glioma models, Clin. Cancer Res. 27 (15) (2021) 4325–4337, https://doi.org/10.1158/1078-0432.CCR-20-3760.
[129] H. Shan, G. Zheng, S. Bao, H. Yang, U.D. Shrestha, G. Li, X. Duan, X. Du, T. Ke, C. Liao, Tumor perfusion enhancement by focus ultrasound-induced blood-brain barrier opening to potentiate anti-PD-1 immunotherapy of glioma, Transl Oncol 49 (2024) 102115, https://doi.org/10.1016/j.tranon.2024.102115.
[130] G. Rao, K. Latha, M. Ott, A. Sabbagh, A. Marisetty, X. Ling, D. Zamler, T. A. Doucette, Y. Yang, L.Y. Kong, J. Wei, G.N. Fuller, F. Benavides, A.M. Sonabend, J. Long, S. Li, M. Curran, A.B. Heimberger, Anti-PD-1 induces M1 polarization in the glioma microenvironment and exerts therapeutic efficacy in the absence of CD8 cytotoxic T cells, Clin. Cancer Res. 26 (17) (2020) 4699–4712, https://doi.org/10.1158/1078-0432.CCR-19-4110.
[131] C.D. Arvanitis, V. Askoxylakis, Y. Guo, M. Datta, J. Kloepper, G.B. Ferraro, M. O. Bernabeu, D. Fukumura, N. McDannold, R.K. Jain, Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood-tumor barrier disruption, Proc. Natl. Acad. Sci. USA. 115 (37) (2018) E8717–E8726, https://doi.org/10.1073/pnas.1807105115.
[132] E. Memari, D. Khan, R. Alkins, B. Helfield, Focused ultrasound-assisted delivery of immunomodulating agents in brain cancer, J. Contr. Release 367 (2024) 283–299, https://doi.org/10.1016/j.jconrel.2024.01.034.
[133] K.S. Kim, K. Habashy, A. Gould, J. Zhao, H. Najem, C. Amidei, R. Saganty, V. A. Arrieta, C. Dmello, L. Chen, D.Y. Zhang, B. Castro, L. Billingham, D. Levey, O. Huber, M. Marques, D.A. Savitsky, B.M. Morin, M. Muzzio, M. Canney, C. Horbinski, P. Zhang, J. Miska, S. Padney, B. Zhang, R. Rabadan, J.J. Phillips, N. Butowski, A.B. Heimberger, J. Hu, R. Stupp, D. Chand, C. Lee-Chang, A. M. Sonabend, Fc-enhanced anti-CTLA-4, anti-PD-1, doxorubicin, and ultrasound-mediated blood-brain barrier opening: a novel combinatorial immunotherapy regimen for gliomas, Neuro Oncol. 26 (11) (2024) 2044–2060, https://doi.org/10.1093/neuonc/noae135.
[134] Y.C. Yang, Y. Zhu, S.J. Sun, C.J. Zhao, Y. Bai, J. Wang, L.T. Ma, ROS regulation in gliomas: implications for treatment strategies, Front. Immunol. 14 (2023) 1259797, https://doi.org/10.3389/fimmu.2023.1259797.
[135] L.S. Qin, P.F. Jia, Z.Q. Zhang, S.M. Zhang, ROS-p53-cyclophilin-D signaling mediates salinomycin-induced glioma cell necrosis, J. Exp. Clin. Cancer Res. 34 (1) (2015) 57, https://doi.org/10.1186/s13046-015-0174-1.
[136] S. Son, J.H. Kim, X. Wang, C. Zhang, S.A. Yoon, J. Shin, A. Sharma, M.H. Lee, L. Cheng, J. Wu, J.S. Kim, Multifunctional sonosensitizers in sonodynamic cancer therapy, Chem. Soc. Rev. 49 (11) (2020) 3244–3261, https://doi.org/10.1039/c9cs00648f.
[137] T. Wu, Y. Liu, Y. Cao, Z. Liu, Engineering macrophage exosome disguised biodegradable nanoplatform for enhanced sonodynamic therapy of glioblastoma, Adv. Mater. 34 (15) (2022) e2110364, https://doi.org/10.1002/adma.202110364.
[138] X. Wang, Y. Jia, P. Wang, Q. Liu, H. Zheng, Current status and future perspectives of sonodynamic therapy in glioma treatment, Ultrason. Sonochem. 37 (2017) 592–599, https://doi.org/10.1016/j.ultsonch.2017.02.020.
[139] S. Yamaguchi, H. Kobayashi, T. Narita, K. Kanehira, S. Sonezaki, N. Kudo, Y. Kubota, S. Terasaka, K. Houkin, Sonodynamic therapy using water-dispersed TiO2-polyethylene glycol compound on glioma cells: comparison of cytotoxic mechanism with photodynamic therapy, Ultrason. Sonochem. 18 (5) (2011) 1197–1204, https://doi.org/10.1016/j.ultsonch.2010.12.017.
[140] S. Dai, S. Hu, C. Wu, Apoptotic effect of sonodynamic therapy mediated by hematoporphyrin monomethyl ether on C6 glioma cells in vitro, Acta Neurochir. 151 (12) (2009) 1655–1661, https://doi.org/10.1007/s00701-009-0456-5.
[141] J.H. Li, W. Yue, Z. Huang, Z.Q. Chen, Q. Zhan, F.B. Ren, J.Y. Liu, S.B. Fu, Calcium overload induces C6 rat glioma cell apoptosis in sonodynamic therapy, Int. J. Radiat. Biol. 87 (10) (2011) 1061–1066, https://doi.org/10.3109/09553002.2011.584938.
[142] Z. Chen, J. Li, X. Song, Z. Wang, W. Yue, Use of a novel sonosensitizer in sonodynamic therapy of U251 glioma cells in vitro, Exp. Ther. Med. 3 (2) (2012) 273–278, https://doi.org/10.3892/etm.2011.390.
[143] K. Bilmin, T. Kujawska, W. Secomski, A. Nowicki, P. Grieb, 5-Aminolevulinic acid-mediated sonosensitization of rat RG2 glioma cells in vitro, Folia Neuropathol. 54 (3) (2016) 234–240, https://doi.org/10.5114/fn.2016.62233.
[144] S. Endo, N. Kudo, S. Yamaguchi, K. Sumiyoshi, H. Motegi, H. Kobayashi, S. Terasaka, K. Houkin, Porphyrin derivatives-mediated sonodynamic therapy for

malignant gliomas in vitro, Ultrasound Med. Biol. 41 (9) (2015) 2458–2465, https://doi.org/10.1016/j.ultrasmedbio.2015.05.007.
[145] J.H. Li, D.Y. Song, Y.G. Xu, Z. Huang, W. Yue, In vitro study of haematoporphyrin monomethyl ether-mediated sonodynamic effects on C6 glioma cells, Neurol. Sci. 29 (4) (2008) 229–235, https://doi.org/10.1007/s10072-008-0972-8.
[146] J.H. Li, Z.Q. Chen, Z. Huang, Q. Zhan, F.B. Ren, J.Y. Liu, W. Yue, Z. Wang, In vitro study of low intensity ultrasound combined with different doses of PDT: effects on C6 glioma cells, Oncol. Lett. 5 (2) (2013) 702–706, https://doi.org/10.3892/ol.2012.1060.
[147] F. Prada, N. Sheybani, A. Franzini, D. Moore, D. Cordeiro, J. Sheehan, K. Timbie, Z. Xu, Fluorescein-mediated sonodynamic therapy in a rat glioma model, J. Neuro Oncol. 148 (3) (2020) 445–454, https://doi.org/10.1007/s11060-020-03536-2.
[148] Q.L. Guo, X.L. Dai, M.Y. Yin, H.W. Cheng, H.S. Qian, H. Wang, D.M. Zhu, X. W. Wang, Nanosensitizers for sonodynamic therapy for glioblastoma multiforme: current progress and future perspectives, Mil Med Res 9 (1) (2022) 26, https://doi.org/10.1186/s40779-022-00386-z.
[149] Y. Sun, H. Wang, P. Wang, K. Zhang, X. Geng, Q. Liu, X. Wang, Tumor targeting DVDMS-nanoliposomes for an enhanced sonodynamic therapy of gliomas, Biomater. Sci. 7 (3) (2019) 985–994, https://doi.org/10.1039/c8bm01187g.
[150] J. Li, Z. Yue, M. Tang, W. Wang, Y. Sun, T. Sun, C. Chen, Strategies to reverse hypoxic tumor microenvironment for enhanced sonodynamic therapy, Adv. Healthcare Mater. 13 (1) (2024) e2302028, https://doi.org/10.1002/adhm.202302028.
[151] F. Wang, L. Xu, B. Wen, S. Song, Y. Zhou, H. Wu, Q. Wu, Y. Wang, X. Tong, H. Yan, Ultrasound-excited temozolomide sonosensitization induces necroptosis in glioblastoma, Cancer Lett. 554 (2023) 216033, https://doi.org/10.1016/j.canlet.2022.216033.
[152] Z. Chen, L. Yang, Z. Yang, Z. Wang, W. He, W. Zhang, Disordered convolution region of P(VDF-TrFE) piezoelectric nanoparticles: the core of sono-piezo dynamic therapy, ACS Appl. Mater. Interfaces 15 (46) (2023) 53251–53263, https://doi.org/10.1021/acsami.3c12614.
[153] C. Pucci, A. Marino, Ö. Şen, D. De Pasquale, M. Bartolucci, N. Iturrioz-Rodríguez, N. di Leo, G. de Vito, D. Debellis, A. Petretto, G. Ciofani, Ultrasound-responsive nutlin-loaded nanoparticles for combined chemotherapy and piezoelectric treatment of glioblastoma cells, Acta Biomater. 139 (2022) 218–236, https://doi.org/10.1016/j.actbio.2021.04.005.
[154] M. Rodriguez, A. Kaushik, J. Lapierre, S.M. Dever, N. El-Hage, M. Nair, Electromagnetic nano-particle bound Beclin1 siRNA crosses the blood-brain barrier to attenuate the inflammatory effects of HIV-1 infection in vitro, J. Neuroimmune Pharmacol. 12 (1) (2017) 120–132, https://doi.org/10.1007/s11481-016-9688-3.
[155] X. Huang, L. Gao, W. Ge, S. Li, Y. Liu, X. Fan, S. Tu, F. Wang, An ultrasound-activated piezoelectric sonosensitizer enhances mitochondrial depolarization for effective treatment of orthotopic glioma, Acta Biomater. 190 (2024) 435–446, https://doi.org/10.1016/j.actbio.2024.10.051.
[156] Z. Chen, L. Sang, Y. Liu, Z. Bai, Sono-piezo dynamic therapy: utilizing piezoelectric materials as sonosensitizer for sonodynamic therapy, Adv. Sci. (2025) e2417439, https://doi.org/10.1002/advs.202417439.
[157] M. Montorsi, C. Pucci, D. De Pasquale, A. Marino, M.C. Ceccarelli, M. Mazzuferi, M. Bartolucci, A. Petretto, M. Prato, D. Debellis, G. De Simoni, G. Pugliese, M. Labardi, G. Ciofani, Ultrasound-activated piezoelectric nanoparticles trigger microglia activity against glioblastoma cells, Adv. Healthcare Mater. 13 (18) (2024) e2304331, https://doi.org/10.1002/adhm.202304331.
[158] P. Zhu, Y. Chen, J. Shi, Nanoenzyme-augmented cancer sonodynamic therapy by catalytic tumor oxygenation, ACS Nano 12 (4) (2018) 3780–3795, https://doi.org/10.1021/acsnano.8b00999.
[159] C.H. Fan, C.Y. Ting, H.J. Lin, C.H. Wang, H.L. Liu, T.C. Yen, C.K. Yeh, SPIO-conjugated, doxorubicin-loaded microbubbles for concurrent MRI and focused-ultrasound enhanced brain-tumor drug delivery, Biomaterials 34 (14) (2013) 3706–3715, https://doi.org/10.1016/j.biomaterials.2013.01.099.
[160] L. Chen, D. Cong, Y. Li, D. Wang, Q. Li, S. Hu, Combination of sonodynamic with temozolomide inhibits C6 glioma migration and promotes mitochondrial pathway apoptosis via suppressing NHE-1 expression, Ultrason. Sonochem. 39 (2017) 654–661, https://doi.org/10.1016/j.ultsonch.2017.05.013.
[161] S.J. Madsen, J. Gonzales, G. Zamora, K. Berg, R.K. Nair, H. Hirschberg, Comparing the effects of light- or sonic-activated drug delivery: photochemical/sonochemical internalization, J. Environ. Pathol. Toxicol. Oncol. 35 (1) (2016) 91–98, https://doi.org/10.1615/JEnvironPatholToxicolOncol.2016015463.
[162] X. Wang, F. Yan, X. Liu, P. Wang, S. Shao, Y. Sun, Z. Sheng, Q. Liu, J.F. Lovell, H. Zheng, Enhanced drug delivery using sonoactivatable liposomes with membrane-embedded porphyrins, J. Contr. Release 286 (2018) 358–368, https://doi.org/10.1016/j.jconrel.2018.07.048.
[163] Y.H. Chen, D. Moore, C.C. Lee, Y.H. Su, Focused ultrasound for brain metastases: an update on global clinical trials, J. Neuro Oncol. 165 (1) (2023) 53–62, https://doi.org/10.1007/s11060-023-04492-3.
[164] M. Ishikawa, Y. Ota, M. Nagai, G. Kusaka, Y. Tanaka, H. Naritaka, Ultrasonography monitoring with superb microvascular imaging technique in brain tumor surgery, World Neurosurg 97 (2017) 749.e11–749.e20, https://doi.org/10.1016/j.wneu.2016.10.111.
[165] D.R. Johnson, J.B. Guerin, M.W. Ruff, S. Fang, C.H. Hunt, J.M. Morris, P. Pearse Morris, T.J. Kaufmann, Glioma response assessment: classic pitfalls, novel confounders, and emerging imaging tools, Br. J. Radiol. 92 (1094) (2019) 20180730, https://doi.org/10.1259/bjr.20180730.
[166] F. Prada, V. Vitale, M. Del Bene, C. Boffano, L.M. Sconfienza, V. Pinzi, G. Mauri, L. Solbiati, G. Sakas, V. Kolev, L. D'Incerti, F. DiMeco, Contrast-enhanced MR imaging versus contrast-enhanced US: a comparison in glioblastoma surgery by using intraoperative fusion imaging, Radiology 285 (1) (2017) 242–249, https://doi.org/10.1148/radiol.2017161206.
[167] H.L. Liu, H.W. Yang, M.Y. Hua, K.C. Wei, Enhanced therapeutic agent delivery through magnetic resonance imaging-monitored focused ultrasound blood-brain barrier disruption for brain tumor treatment: an overview of the current preclinical status, Neurosurg. Focus 32 (1) (2012) E4, https://doi.org/10.3171/2011.10.FOCUS11238.
[168] P. Anastasiadis, D. Gandhi, Y. Guo, A.K. Ahmed, S.M. Bentzen, C. Arvanitis, G. F. Woodworth, Localized blood-brain barrier opening in infiltrating gliomas with MRI-guided acoustic emissions-controlled focused ultrasound, Proc. Natl. Acad. Sci. U. S. A. 118 (37) (2021) e2103280118, https://doi.org/10.1073/pnas.2103280118.
[169] S.Y. Wu, C. Aurup, C.S. Sanchez, J. Grondin, W. Zheng, H. Kamimura, V. P. Ferrera, E.E. Konofagou, Efficient blood-brain barrier opening in primates with neuronavigation-guided ultrasound and real-time acoustic mapping, Sci. Rep. 8 (1) (2018) 7978, https://doi.org/10.1038/s41598-018-25904-9.
[170] K.C. Wei, H.C. Tsai, Y.J. Lu, H.W. Yang, M.Y. Hua, M.F. Wu, P.Y. Chen, C. Y. Huang, T.C. Yen, H.L. Liu, Neuronavigation-guided focused ultrasound-induced blood-brain barrier opening: a preliminary study in swine, AJNR Am J Neuroradiol 34 (1) (2013) 115–120, https://doi.org/10.3174/ajnr.A3150.
[171] K.T. Chen, W.Y. Chai, Y.J. Lin, C.J. Lin, P.Y. Chen, H.C. Tsai, C.Y. Huang, J.S. Kuo, H.L. Liu, K.C. Wei, Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors, Sci. Adv. 7 (6) (2021 Feb 5) eabd0772, https://doi.org/10.1126/sciadv.abd0772. PMID: 33547073; PMCID: PMC7864566.
[172] J. Yuan, L. Xu, C.Y. Chien, Y. Yang, Y. Yue, S. Fadera, A.H. Stark, K.E. Schwetye, A. Nazeri, R. Desai, U. Athiraman, A.A. Chaudhuri, H. Chen, E.C. Leuthardt, First-in-human prospective trial of sonobiopsy in high-grade glioma patients using neuronavigation-guided focused ultrasound, npj Precis. Oncol. 7 (1) (2023) 92, https://doi.org/10.1038/s41698-023-00448-y.
[173] S. Bae, K. Liu, A.N. Pouliopoulos, R. Ji, E.E. Konofagou, Real-time passive acoustic mapping with enhanced spatial resolution in neuronavigation-guided focused ultrasound for blood-brain barrier opening, IEEE Trans. Biomed. Eng. 70 (10) (2023) 2874–2885, https://doi.org/10.1109/TBME.2023.3266952.
[174] A. Yildirim, N.T. Blum, A.P. Goodwin, Colloids, nanoparticles, and materials for imaging, delivery, ablation, and theranostics by focused ultrasound (FUS), Theranostics 9 (9) (2019) 2572–2594, https://doi.org/10.7150/thno.32424.
[175] M.G. Shapiro, P.W. Goodwill, A. Neogy, M. Yin, F.S. Foster, D.V. Schaffer, S. M. Conolly, Biogenic gas nanostructures as ultrasonic molecular reporters, Nat. Nanotechnol. 9 (4) (2014) 311–316, https://doi.org/10.1038/nnano.2014.32.
[176] D. Maresca, T. Payen, A. Lee-Gosselin, B. Ling, D. Malounda, C. Demené, M. Tanter, M.G. Shapiro, Acoustic biomolecules enhance hemodynamic functional ultrasound imaging of neural activity, Neuroimage 209 (2020) 116467, https://doi.org/10.1016/j.neuroimage.2019.116467.
[177] C.T.W. Moonen, J.P. Kilroy, A.L. Klibanov, Focused ultrasound: noninvasive image-guided therapy, Investig. Radiol. 60 (3) (2025) 205–219, https://doi.org/10.1097/RLI.0000000000001116.
[178] Y. Liu, H. Liu, H. Yan, Y. Liu, J. Zhang, W. Shan, P. Lai, H. Li, L. Ren, Z. Li, L. Nie, Aggregation-induced absorption enhancement for deep near-infrared II photoacoustic imaging of brain gliomas in vivo, Adv. Sci. 6 (8) (2019 Jan 16) 1801615, https://doi.org/10.1002/advs.201801615. PMID: 31016108; PMCID: PMC6469237.
[179] S. Liang, D. Hu, G. Li, D. Gao, F. Li, H. Zheng, M. Pan, Z. Sheng, NIR-II fluorescence visualization of ultrasound-induced blood-brain barrier opening for enhanced photothermal therapy against glioblastoma using indocyanine green microbubbles, Sci. Bull. 67 (22) (2022) 2316–2326, https://doi.org/10.1016/j.scib.2022.10.025.
[180] Y. Liu, Y. Li, S. Koo, Y. Sun, Y. Liu, X. Liu, Y. Pan, Z. Zhang, M. Du, S. Lu, X. Qiao, J. Gao, X. Wang, Z. Deng, X. Meng, Y. Xiao, J.S. Kim, X. Hong, Versatile types of inorganic/organic NIR-IIa/IIb fluorophores: from strategic design toward molecular imaging and theranostics, Chem. Rev. 122 (1) (2022) 209–268, https://doi.org/10.1021/acs.chemrev.1c00553.
[181] Z. Sheng, B. Guo, D. Hu, S. Xu, W. Wu, W.H. Liew, K. Yao, J. Jiang, C. Liu, H. Zheng, B. Liu, Bright aggregation-induced-emission dots for targeted synergetic NIR-II fluorescence and NIR-I photoacoustic imaging of orthotopic brain tumors, Adv. Mater. (2018) e1800766, https://doi.org/10.1002/adma.201800766.
[182] B. Guo, Z. Feng, D. Hu, S. Xu, E. Middha, Y. Pan, C. Liu, H. Zheng, J. Qian, Z. Sheng, B. Liu, Precise deciphering of brain vasculatures and microscopic tumors with dual NIR-II fluorescence and photoacoustic imaging, Adv. Mater. 31 (30) (2019) e1902504, https://doi.org/10.1002/adma.201902504.
[183] D. Gao, Y. Li, Y. Wu, Y. Liu, D. Hu, S. Liang, J. Liao, M. Pan, P. Zhang, K. Li, X. Liu, H. Zheng, Z. Sheng, Albumin-consolidated AIEgens for boosting glioma and cerebrovascular NIR-II fluorescence imaging, ACS Appl. Mater. Interfaces 15 (1) (2023) 3–13, https://doi.org/10.1021/acsami.1c22700.
[184] P. Liu, S. Lan, D. Gao, D. Hu, Z. Chen, Z. Li, G. Jiang, Z. Sheng, Targeted blood-brain barrier penetration and precise imaging of infiltrative glioblastoma margins using hybrid cell membrane-coated ICG liposomes, J. Nanobiotechnol. 22 (1) (2024) 603, https://doi.org/10.1186/s12951-024-02870-1.
[185] H.M. Duvernoy, S. Delon, J.L. Vannson, Cortical blood vessels of the human brain, Brain Res. Bull. 7 (5) (1981) 519–579, https://doi.org/10.1016/0361-9230(81)90007-1.
[186] O. Jung, A. Thomas, S.R. Burks, M.L. Dustin, J.A. Frank, M. Ferrer, E. Stride, Neuroinflammation associated with ultrasound-mediated permeabilization of the blood-brain barrier, Trends Neurosci. 45 (6) (2022) 459–470, https://doi.org/10.1016/j.tins.2022.03.003.

[187] Y. Zhang, J. Wang, S.N. Ghobadi, H. Zhou, A. Huang, M. Gerosa, Q. Hou, O. Keunen, A. Golebiewska, F.G. Habte, G.A. Grant, R. Paulmurugan, K.S. Lee, M. Wintermark, Molecular identity changes of tumor-associated macrophages and microglia after magnetic resonance imaging-guided focused ultrasound-induced blood-brain barrier opening in a mouse glioblastoma model, Ultrasound Med. Biol. 49 (5) (2023) 1082–1090, https://doi.org/10.1016/j.ultrasmedbio.2022.12.006.

[188] C. Poon, C. Pellow, K. Hynynen, Neutrophil recruitment and leukocyte response following focused ultrasound and microbubble mediated blood-brain barrier treatments, Theranostics 11 (4) (2021) 1655–1671, https://doi.org/10.7150/thno.52710.

[189] H.J. Choi, M. Han, H. Seo, C.Y. Park, E.H. Lee, J. Park, The new insight into the inflammatory response following focused ultrasound-mediated blood-brain barrier disruption, Fluids Barriers CNS 19 (1) (2022) 103, https://doi.org/10.1186/s12987-022-00402-3.

[190] D. McMahon, K. Hynynen, Acute inflammatory response following increased blood-brain barrier permeability induced by focused ultrasound is dependent on microbubble dose, Theranostics 7 (16) (2017) 3989–4000, https://doi.org/10.7150/thno.21630.

[191] C.H. Tsai, J.W. Zhang, Y.Y. Liao, H.L. Liu, Real-time monitoring of focused ultrasound blood-brain barrier opening via subharmonic acoustic emission detection: implementation of confocal dual-frequency piezoelectric transducers, Phys. Med. Biol. 61 (7) (2016) 2926–2946, https://doi.org/10.1088/0031-9155/61/7/2926.

[192] R. Ji, M.E. Karakatsani, M. Burgess, M. Smith, M.F. Murillo, E.E. Konofagou, Cavitation-modulated inflammatory response following focused ultrasound blood-brain barrier opening, J. Contr. Release 337 (2021) 458–471, https://doi.org/10.1016/j.jconrel.2021.07.042.

[193] D. McMahon, W. Oakden, K. Hynynen, Investigating the effects of dexamethasone on blood-brain barrier permeability and inflammatory response following focused ultrasound and microbubble exposure, Theranostics 10 (4) (2020) 1604–1618, https://doi.org/10.7150/thno.40908.

[194] M. López-Aguirre, M. Castillo-Ortiz, A. Viña-González, J. Blesa, J.A. Pineda-Pardo, The road ahead to successful BBB opening and drug-delivery with focused ultrasound, J. Contr. Release 372 (2024) 901–913, https://doi.org/10.1016/j.jconrel.2024.07.006.

[195] H. Chen, J. Ji, L. Zhang, T. Chen, Y. Zhang, F. Zhang, J. Wang, Y. Ke, Inflammatory responsive neutrophil-like membrane-based drug delivery system for post-surgical glioblastoma therapy, J. Contr. Release 362 (2023) 479–488, https://doi.org/10.1016/j.jconrel.2023.08.020.

[196] H. Zhu, C. Allwin, M.G. Bassous, A.N. Pouliopoulos, Focused ultrasound-mediated enhancement of blood-brain barrier permeability for brain tumor treatment: a systematic review of clinical trials, J. Neuro Oncol. 170 (2) (2024) 235–252, https://doi.org/10.1007/s11060-024-04795-z.

[197] S. Farzad Maroufi, M. Sadegh Fallahi, S. Parmis Maroufi, J.P. Sheehan, Focused ultrasound blood-brain barrier disruption in high-grade gliomas: scoping review of clinical studies, J. Clin. Neurosci. 128 (2024) 110786, https://doi.org/10.1016/j.jocn.2024.110786.

[198] V.M. Lu, T.N. Niazi, Clinical trials of focused ultrasound for brain tumors, Cancers 17 (3) (2025) 513, https://doi.org/10.3390/cancers17030513.

[199] S. Liao, M. Cai, R. Zhu, T. Fu, Y. Du, J. Kong, Y. Zhang, C. Qu, X. Dong, J. Ni, X. Yin, Antitumor Effect of Photodynamic Therapy/Sonodynamic Therapy/Sono-Photodynamic Therapy of Chlorin e6 and Other Applications, Mol. Pharm. 20 (2) (2023) 875–885, https://doi.org/10.1021/acs.molpharmaceut.2c00824.

[200] Q. Wang, Y. Tian, M. Yao, J. Fu, L. Wang, Y. Zhu, Bimetallic organic frameworks of high piezovoltage for sono-piezo dynamic therapy, Adv. Mater. 35 (41) (2023) e2301784, https://doi.org/10.1002/adma.202301784.

[201] J. Yang, Y. Du, Y. Yao, Y. Liao, B. Wang, X. Yu, K. Yuan, Y. Zhang, F. He, P. Yang, Employing piezoelectric Mg2+-doped hydroxyapatite to target death receptor-mediated necroptosis: a strategy for amplifying immune activation, Adv. Sci. 11 (13) (2024) e2307130, https://doi.org/10.1002/advs.202307130.

[202] Y. Fan, J. Ye, Y. Kang, G. Niu, J. Shi, X. Yuan, R. Li, J. Han, X. Ji, Biomimetic piezoelectric nanomaterial-modified oral microrobots for targeted catalytic and immunotherapy of colorectal cancer, Sci. Adv. 10 (19) (2024) eadm9561, https://doi.org/10.1126/sciadv.adm9561. Epub 2024 May 8.

[203] C. Adams, R.M. Jones, S.D. Yang, W.M. Kan, K. Leung, Y. Zhou, K.U. Lee, Y. Huang, K. Hynynen, Implementation of a skull-conformal phased array for transcranial focused ultrasound therapy, IEEE Trans. Biomed. Eng. 68 (11) (2021) 3457–3468, https://doi.org/10.1109/TBME.2021.3077802.

[204] Z. Deng, Z. Sheng, F. Yan, Ultrasound-induced blood-brain-barrier opening enhances anticancer efficacy in the treatment of glioblastoma: current status and future prospects, J Oncol 2019 (2019) 2345203, https://doi.org/10.1155/2019/2345203.

[205] L. Lamsam, E. Johnson, I.D. Connolly, M. Wintermark, M. Hayden Gephart, A review of potential applications of MR-guided focused ultrasound for targeting brain tumor therapy, Neurosurg. Focus 44 (2) (2018) E10, https://doi.org/10.3171/2017.11.FOCUS17620.

[206] D. Coluccia, C.A. Figueiredo, M.Y. Wu, A.N. Riemenschneider, R. Diaz, A. Luck, C. Smith, S. Das, C. Ackerley, M. O'Reilly, K. Hynynen, J.T. Rutka, Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound, Nanomedicine 14 (4) (2018) 1137–1148, https://doi.org/10.1016/j.nano.2018.01.021.

[207] M.C. Javitt, A. Kravtsov, Z. Keidar, S. Abadi, G.E. Amiel, Multimodality image fusion with PSMA PET/CT and high-intensity focused ultrasound focal therapy for primary diagnosis and management of prostate cancer: a planned research initiative, Rambam Maimonides Med J 8 (4) (2017) e0037, https://doi.org/10.5041/RMMJ.10312.