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Editorial: The blood-brain barrier in brain tumors: molecular mechanisms and therapeutic strategies

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Editorial on the Research Topic

[The blood-brain barrier in brain tumors: molecular mechanisms and therapeutic strategies](#)

The blood-brain barrier (BBB) is a specialization of brain endothelial cells (ECs) that hinders the effective delivery of drugs into the brain by establishing EC junctions, sealing EC-EC contacts, pumping drugs out by active transport, and suppressing transcytosis (1, 2). In brain tumors, blood vessels are abnormal with a heterogeneous and partially intact BBB, known as the blood-tumor barrier (BTB) (1, 3). The extremely limited systemic therapeutic options after surgery and radiotherapy are one of the culprits for the dismal prognosis in brain tumor patients. Brain tumors can only be cured if the tumor cells hidden behind the BBB are adequately treated (4–6). This Editorial will review current issues in addressing the BBB and, more specifically, introduce four manuscripts included in this Research Topic.

Opening of the BBB by the FUS technique

The potential of opening the BBB using focused ultrasound (FUS) has received intense interest as a tool to aid the delivery of therapeutic drugs into lesions of the central nervous system (CNS). FUS is a non-invasive therapeutic tool that can induce both thermal ablation and a transient opening of the BBB/BTB. FUS utilizes a special concave transducer, lens, or phased array to converge ultrasound waves into a millimeter-sized precise focal region. BBB/BTB can be transiently opened for access to therapeutics in the brain using FUS targeting intravenously administered microbubbles (MBs). The MBs will oscillate with expansions and contractions during the compression and rarefaction phases of the ultrasound pressure wave in the vasculature. The constantly changing morphology and oscillation of MBs result in shear stress on endothelial cells, which sufficiently breaks tightly sealed junctions in the BBB/BTB by mechanical forces. Mungur et al. provide a systematic review of the opening of the BBB by FUS to enhance drug delivery in glioblastoma (GBM) treatment, together with a comprehensive summary of FUS application in preclinical studies

with animal GBM models and recent clinical trials in GBM patients. [Thombre et al.](#) reviewed currently used methods for FUS-mediated BBB openings in rodent GBM models and proposed standard parameters for BBB opening with high efficiency and low side effects.

The role of nanodelivery systems in brain therapies

Nanodelivery systems are increasingly being developed using various strategies to enhance BBB penetration and accumulation in the brain parenchyma. Extensive efforts have been made to successfully improve the transport of nanomaterials across the BBB through, for example, receptor-mediated transcytosis and shutter peptide-mediated BBB-crossing. In addition, changing characteristic properties of nanomaterials, including particle size, composition, hydrophobicity, charge, and dissociation degree, provides a broad space for researchers to modify the system, developing more promising strategies for nanomaterial-based BBB crossing. [Liu et al.](#) summarized available nanodelivery systems for non-permeable phytochemicals to the CNS, boosting novel applications of nanodelivery for brain diseases.

[Semyachkina-Glushkovskaya et al.](#) provide evidence that music induces BBB opening via the brain drainage system, improving the therapeutic effects of bevacizumab in a rat GBM model. This study sheds new light on the application of music therapy for the treatment of malignant brain tumors.

Altogether, this Research Topic presents recent advances in strategies to improve drug delivery across the BBB, facilitating the design and application of novel therapeutic strategies for GBM treatment.

References

- Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nat Rev Cancer*. (2020) 20:26–41. doi: 10.1038/s41568-019-0205-x
- Walchli T, Bisschop J, Carmeliet P, Zadeh G, Monnier PP, De Bock K, et al. Shaping the brain vasculature in development and disease in the single-cell era. *Nat Rev Neurosci*. (2023) 24:271–98. doi: 10.1038/s41583-023-00684-y
- Xie Y, He L, Lugano R, Zhang Y, Cao H, He Q, et al. Key molecular alterations in endothelial cells in human glioblastoma uncovered through single-cell RNA sequencing. *JCI Insight*. (2021) 6:61. doi: 10.1172/jci.insight.150861
- Xie Y, He L, Zhang Y, Huang H, Yang F, Chao M, et al. Wnt signaling regulates MFSD2A-dependent drug delivery through endothelial transcytosis in glioma. *Neuro Oncol*. (2023) 25:1073–84. doi: 10.1093/neuonc/noac288
- Griveau A, Seano G, Shelton SJ, Kupp R, Jahangiri A, Obernier K, et al. A glial signature and wnt7 signaling regulate glioma-vascular interactions and tumor microenvironment. *Cancer Cell*. (2018) 33:874–89. doi: 10.1016/j.ccell.2018.03.020
- Phoenix TN, Patmore DM, Boop S, Boulos N, Jacus MO, Patel YT, et al. Medulloblastoma genotype dictates blood brain barrier phenotype. *Cancer Cell*. (2016) 29:508–22. doi: 10.1016/j.ccell.2016.03.002

Author contributions

LZ contributed to organizing the topic review and wrote the manuscript. AD and JR polished and revised the editorial. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

JR was employed by Spark Therapeutics Inc.

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