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Advances in Blood-brain Barrier Permeability Modulation for Targeted Drug Delivery in Neuro-oncology

Della Leroy*

Department of Oncology, Assiut University, Egypt

INTRODUCTION

The Blood-brain Barrier (BBB) is a highly selective, semipermeable membrane that protects the Central Nervous System (CNS) by preventing the entry of harmful substances from the bloodstream. While critical for maintaining neural homeostasis, the BBB presents a significant obstacle to the delivery of therapeutic agents for neuro-oncological conditions, particularly brain tumors like glioblastoma. Conventional therapies often fail to achieve adequate concentrations in the brain, leading to suboptimal treatment outcomes. To address this challenge, researchers have developed innovative strategies to modulate BBB permeability and facilitate targeted drug delivery. The BBB comprises tightly packed endothelial cells, astrocytic end-feet, and a basement membrane, forming a robust defense mechanism. It restricts the passage of large molecules, proteins, and over 98% of small-molecule drugs. This protection, while beneficial against toxins and pathogens, becomes a barrier to effective treatment in brain cancer. Furthermore, brain tumors themselves can alter the BBB's integrity, creating heterogeneous permeability that complicates therapeutic delivery. Focused ultrasound, combined with microbubbles, has emerged as a promising technique to transiently and reversibly disrupt the BBB. The ultrasound waves cause the microbubbles to oscillate within the brain's vasculature, temporarily loosening tight junctions between endothelial cells. This allows drugs to penetrate the CNS more effectively.

DESCRIPTION

Clinical trials have demonstrated the safety of FUS in patients with glioblastoma, with ongoing research optimizing its use for chemotherapy and immunotherapy delivery. Nano Particles (NPs) have shown great potential in crossing the BBB due to their small size and modifiable surface properties. These systems can be engineered to encapsulate therapeutic agents and enhance their delivery to brain tumors. Lipid-based nanoparticles can be functionalized with ligands that target overexpressed receptors on the BBB, improving specificity. Polymers like PLGA (Poly-Lactic-co-Glycolic Acid) provide controlled drug release and increased BBB penetration. Naturally derived nanoscale vesicles can carry drugs across the BBB with minimal immune response. Chemical agents such as bradykinin analogs (e.g., RMP-7) or hyperosmotic solutions like mannitol can transiently open the BBB by disrupting tight junctions. These methods have been used to enhance the delivery of chemotherapeutic agents, although their nonspecific effects remain a concern. Leveraging natural transport mechanisms within the BBB, RMT involves attaching drugs to ligands that bind to specific endothelial cell receptors (e.g., transferrin or insulin receptors). This strategy enables the transport of large therapeutic molecules, including monoclonal antibodies and peptides, across the BBB.

CONCLUSION

The future of BBB modulation lies in the integration of multiple approaches to enhance therapeutic efficacy while minimizing risks. Combination strategies, such as FUS combined with nanoparticles or receptor-mediated delivery systems, are being explored to improve drug targeting. Additionally, advancements in imaging and real-time monitoring will enable precise modulation of the BBB, ensuring that treatments reach their intended targets. Advances in BBB permeability modulation have revolutionized the landscape of targeted drug delivery in neuro-oncology. Techniques such as focused ultrasound, nanotechnology, and receptor-mediated transport are paving the way for more effective and precise treatments for brain tumors. While challenges remain, the ongoing integration of engineering, molecular biology, and clinical research holds the promise of transforming outcomes for patients with neuro-oncological diseases, bringing us closer to a new era in brain cancer therapy.

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Corresponding author Della Leroy, Department of Oncology, Assiut University, Egypt, E-mail: dellaleroy@yahoo.com

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