Molecular Therapy
Nucleic Acids
Commentary

Targeted nucleic acid delivery for traumatic brain injury: Overcoming blood-brain barrier challenges

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Traumatic brain injury (TBI) is a challenging clinical problem and a leading cause of death and disability in children and adolescents. Each year, millions of people suffer from TBI due to accidents, sports, and military conflicts. TBIs have complex pathophysiology and can further develop over time, posing challenges in finding suitable treatment methods. In addition to primary injuries, secondary injury mechanisms, including the production of inflammatory cytokines, neutrophil infiltration, excitotoxicity of glutamate, formation of free radicals, cell apoptosis, and scar formation, contribute to the expansion of damage. Therefore, attenuating the focal pro-inflammatory microenvironment is crucial for alleviating secondary damage to the blood-brain barrier (BBB) and improving prognosis.

Xiao et al. herein reported a strategy of using lipid-based carriers to deliver small interfering RNA (siRNA) of Toll-like receptor 4 (TLR4) to astrocytes, leading to a significant decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines in the serum. Moreover, this method could mitigate the disruption of the BBB, reducing the secondary damage caused by TBI.[1] To this end, adenosine-functionalized lipids were incorporated into lipid nanoparticles (LNPs) to enhance their affinity to astrocytes. Astrocytes are the predominant glial cell type in the central nervous system (CNS) and express all four subtypes of adenosine receptors (ARs) on their surface. Furtermore, ionizable group-functionalized lipids were introduced into LNPs to enhance siRNA delivery efficiency to astrocytes, regulating their inflammatory phenotype to maintain the BBB integrity and alleviate secondary brain injury.

This study revives readers' concerns over the challenges brought about by the BBB. As mentioned in the discussed section, the CNS of TBI mice is marked by a severe inflammatory response induced by activated astrocytes and microglia, which disrupts and increases the permeability of the BBB. This study has leveraged this characteristic to enable LNPs to penetrate the BBB. However, in some CNS diseases, the BBB does not exhibit the same permeability as in TBI, necessitating particular drug delivery strategies to tackle the BBB challenge. Morever, in TBI models, when the BBB is restored as a consequence of a valid treatment, we must explore how to help the drug cross the BBB effectively if the medication is still required.

Numerous innovative strategies and delivery vehicles have been developed to address BBB challenges for enhancing nucleic acid delivery efficacy to the CNS.[2] Chen's team utilized focused-ultrasound-mediated intranasal delivery (FUSIN) to deliver adeno-associated virus (AAV)-encapsulated nucleic acid drugs to the brain.[3] They delivered AAV serotype 5 (AAV5-hSyn-EGFP) carrying green fluorescent protein (GFP) to the cerebral cortex and brainstem using focused ultrasound and microbubbles. This strategy shows excellent promise in bypassing the BBB for viral vectors and potential applications in other delivery systems. Furthermore, in another study, lipid molecules are conjugated with neurotransmitters and integrated into drug-loaded LNPs, allowing them to traverse the BBB effectively.[4] These LNPs can be administered via intravenous injection, facilitating drug transport across the barrier and subsequent fusion with neurons and other cells in the brain to deliver therapeutic payloads. Utilizing such systems has successfully achieved functional gene silencing or gene recombination.

While the aforementioned studies have provided valuable insights into addressing the challenges the BBB poses, it is crucial to acknowledge that long-term drug administration is often necessary for treating CNS diseases.[5] However, repeated administrations may potentially cause harm to the BBB. Therefore, the development of a delivery system capable of crossing the BBB while ensuring sustained release of therapeutic molecules becomes imperative. Alvarez-Erviti et al. conducted a noteworthy study in which they modified dendritic cell-derived extracellular vehicles (EVs) with the rabies virus glycoprotein (RVG) peptide, specifically targeting acetylcholine receptors (AChRs).[6] This modification enabled EVs to transport drugs across the BBB efficiently to treat brain diseases. Building upon this approach, Yao's group has made significant advancements by employing circular RNA (circRNA) delivery methods to alleviate depressive-like behavior and stroke in mice.[7] Notably, using vesicles allows for effective penetration of the BBB, while the inherent stability of circRNA, owing to its covalently closed circular structure, safeguards it against degradation by exonucleases.[8] Consequently, this approach facilitates the sustained production of therapeutic molecules, meeting the long-term drug delivery requirements for CNS diseases without needing multiple administrations.

Current remarkable progress in nucleic acid drug delivery has paved the way for treating

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CNS diseases. With the continuous exploration of intricate gene regulation and molecular pathways, it is conceivable that nucleic acid drugs, especially circRNA, will play a key role in treating various neurological disorders. As drug delivery systems and targeting methods advance, we can anticipate breakthroughs in personalized medicine, where tailor-made nucleic acid therapies will provide precise and effective treatments for patients with CNS diseases.

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AUTHOR CONTRIBUTIONS

J.Z. prepared the original draft, and J.C. reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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