Extracellular vesicle-based gene therapy for neurodegenerative diseases

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Neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD) involve progressive neuron deterioration and multisystem malfunctions, profoundly impacting quality of life and survival. A major barrier to effective therapy is the challenge of delivering therapeutics across the blood brain barrier (BBB) to the central nervous system (CNS). While current strategies rely on invasive intrathecal or intraventricular administration, these methods pose risks such as spinal cord and nerve injury, infection, or cerebrospinal fluid leakage. Less invasive systemic delivery remains inefficient due to the restrictive nature of the BBB, particularly for macromolecules like antisense oligonucleotides (ASOs), peptides, and small interfering RNAs (siRNAs). We propose to develop extracellular vesicles (EVs) derived from neural stem cells (NSCs) as a systemic delivery platform for CNS-targeted therapies. EVs are nanosized, naturally occurring carriers of bioactive molecules, including nucleic acids and proteins, which mediate intercellular communication. Our preliminary data show that NSC-derived EVs (NSC-EVs) can cross the BBB and exhibit anti-neuroinflammatory and neuroprotective effects in cellular and mouse ALS models. We optimized the loading of therapeutic ASOs, peptides, and CRISPR components into EVs to enhance CNS targeting. Ongoing studies are evaluating the therapeutic efficacy of these EV-mediated gene therapy in both cellular and mouse models of ALS and PD. This work addresses a critical barrier in CNS drug delivery by harnessing the unique targeting and therapeutic properties of NSC-EVs. Our goal is to establish a safe and efficient platform for gene therapy in neurodegenerative diseases, advancing its translational potential toward clinical application.