Lipid Metabolism-Driven CNS Repair via Targeted EV Delivery

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A labile bioactive lipid mediator has emerged as a potential effector of neuroregeneration, but its therapeutic application is constrained by rapid instability and undesirable systemic inflammatory activity. Here, we describe an engineered extracellular vesicle (EV)-based delivery strategy designed to stabilize and localize this lipid-associated activity to sites of hippocampal injury, resulting in recovery of neuronal integrity and cognitive performance. EVs derived from EP4 antagonist-primed mesenchymal stem cells (GWEVs) showed enhanced secretion and selective enrichment of bioactive lipid cargo, including a reparative lipid-associated signal that promoted neuroregeneration, reduced gliosis, and improved spatial memory. Mechanistic studies indicated that the observed therapeutic effect relied not primarily on conventional surface receptor signaling, but rather on intracellular metabolic processing within recipient neurons. Consistent with this model, a structurally stabilized analogue failed to reproduce the beneficial effects, supporting the importance of metabolic turnover for activity. To facilitate translational development, we also established a bioorthogonal click-labeling approach that enabled real-time SPECT imaging of EV biodistribution while preserving function. In vivo imaging demonstrated preferential accumulation of GWEVs in the injured hippocampus, consistent with targeted delivery. Collectively, these findings reveal a previously unappreciated lipid metabolism-dependent mechanism of CNS repair and support the feasibility of using EVs to deliver unstable bioactive lipid cargoes for regenerative applications. This work provides a conceptual and translational framework for developing EV-based strategies for neurodegenerative disorders and traumatic brain injury.