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Brain-Derived Extracellular Vesicle Isolation from Plasma Using Lipid Nanoprobe Technology for CNS Biomarker Discovery

Background: Extracellular vesicles (EVs) circulating in blood carry tissue-specific RNA cargo, including transcripts originating from the central nervous system (CNS). Detecting brain-derived EVs in peripheral blood offers a minimally invasive liquid biopsy approach for accessing neural molecular signatures relevant to substance use disorders. However, isolating brain-derived EV populations from the heterogeneous circulating EV pool remains technically challenging.

Methods: We developed a magnetic bead-based “lipid nanoprobe” approach to isolate brain-derived EVs from human plasma samples (n=19). RNA sequencing was performed on isolated EVs, and brain-derived transcripts were systematically identified by cross-referencing with GTEx tissue expression data. Cell type-specific markers for neurons, astrocytes, oligodendrocytes, microglia, and synaptic compartments were analyzed to characterize the neural cell origins of EV cargo.

Results: Of the transcripts detected, 1,903 (3.0%) were classified as brain-specific, with 700 demonstrating high brain enrichment. Brain-derived transcripts contributed 0.9–11.0% of total expression across samples (mean: 3.15%), indicating successful enrichment of CNS-origin vesicles. Key neuronal markers included NRG1 (35-fold brain enrichment), SNCA (7-fold), and SNAP25 (133-fold). Glial cell markers were robustly detected, including astrocyte markers (GFAP, SLC1A2, AQP4), oligodendrocyte markers (MBP, MOBP, MOG, PLP1), and microglial markers (P2RY12, TREM2). The detection of markers spanning multiple neural cell types confirms successful capture of brain-derived EV populations using the lipid nanoprobe methodology.

Conclusions: Lipid nanoprobe isolation coupled with RNA sequencing reliably captures brain-derived EVs from plasma, detecting transcripts representing diverse neural cell populations including neurons, astrocytes, oligodendrocytes, and microglia. This validated methodology provides a foundation for developing non-invasive liquid biopsy applications to identify CNS biomarkers of substance use disorders, monitor neurotoxicity, and assess treatment response.

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