

Engineered Exosomes Derived from Hypoxic Mesenchymal Stem Cells: Enhanced Blood-Brain Barrier Penetration for Glioblastoma Targeting

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Abstract

Glioblastoma multiforme (GBM) treatment is hindered by the impermeable blood-brain barrier (BBB) and poor drug bioavailability. This study characterizes exosomes isolated from mesenchymal stem cells (MSCs) cultured under 1% O₂ hypoxic conditions and evaluates their BBB transcytosis capabilities. Hypoxic preconditioning significantly enriched exosomal cargo with miR-126 and matrix metalloproteinase-9 (MMP-9), facilitating tight junction modulation in human brain microvascular endothelial cells (hBMECs). Functionalized with chlorotoxin peptides, these engineered exosomes demonstrated 8-fold higher accumulation in orthotopic GBM xenografts compared to normoxic controls. Co-delivery of temozolomide and siRNA against *MGMT* achieved synergistic cytotoxicity in patient-derived GBM spheroids. Our results establish hypoxic MSC-exosomes as a nature-inspired nanocarrier system for brain tumor theranostics.

Keywords: engineered exosomes, hypoxic preconditioning, blood-brain barrier, glioblastoma, miR-126, chlorotoxin targeting



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