TRANSCELLULAR TRAFFICKING OF AMYLOID BETA FROM GUT TO BRAIN IN ALZHEIMER'S DISEASE: A NOVEL INSIGHT INTO DISEASE PATHOGENESIS

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Alzheimer's disease (AD), a leading cause of dementia globally, is primarily characterized by the aggregation of amyloid beta (Aβ) leading to neurodegeneration. However, the precise mechanisms underlying AD remain elusive. This study explores the hypothesis that Aβ seeds can traverse from the gut to the brain, contributing to AD pathology. Utilizing a novel transwell and co-culture model combining intestinal and neuronal cells, and leveraging zebrafish larvae for in vivo imaging, we investigated the transcellular trafficking of Aβ seeds. The integrity of the co-culture model was confirmed through transepithelial electrical resistance measurements and Dextran-FITC assays, indicating robust barrier function. Furthermore, ZO-1 immunostaining revealed tight junction formation, suggesting cell-cell transport of Aβ seeds. Comparative analyses at 4°C and 37°C demonstrated temperature-dependent differences in Aβ trafficking, correlating with active transport mechanisms. Increased reactive oxygen species production and cytotoxicity in neuronal cells were observed upon Aβ seeds uptake from intestinal cells, indicating enhanced neuronal stress. Remarkably, Aβ seeds introduced into the gut of zebrafish larvae was found to migrate to the brain, co-localizing with injected Aβ monomers, thereby supporting the gut-brain axis theory in AD progression. Our findings provide critical insights into the potential role of gut-brain translocation of Aβ in AD, opening new avenues for understanding disease mechanisms and therapeutic intervention.