Novel Blood-derived Extracellular Vesicle-based Biomarkers in Alzheimer’s Disease by the Proximity Extension Assay

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to characterize the EVs of AD patients as a biomarker for disease progression.

**Methods:** Blood samples were collected after obtaining signed informed consent (No. 0462-14-RMB) from 39 AD patients at three stages of disease severity and from 14 healthy controls (HC). Cerebrospinal fluid was collected from five patients and three HC. EV size and concentration were studied by Nano-tracking analysis. Membrane antigens were characterized by their cell origin as defined by flow cytometry. EV protein contents were screened by protein array, and miRNA content was screened by Nano-string technology and validated by RT-PCR.

**Results:** The AD patients’ EVs were significantly smaller and the levels of neural cell markers were higher than EVs obtained from HC. Moderate or severe AD patients’ EVs had a significantly higher level of the Myelin oligodendrocyte glycoprotein (MOG), compared to the EVs obtained from patients with mild AD (P = 0.0002 and P = 0.036). Levels of the EVs that expressed the axonal glycoprotein CD171 were significantly higher in the patients with severe AD compared to HC (P = 0.0066), possibly indicating injured apoptotic neural cells. There was also a significant increase in EVs originating from endothelial cells (labelled with CD31+ CD41-, P = 0.0115 and with CD144, P = 0.0276) in patients with moderate AD compared to EVs obtained from the HC. A >2-fold increase was measured in the content of inflammatory cytokines (TNFα, IL8, IL-2, IFNγ) as was a >50% reduction in growth factors (FGF, EGF VEGF) and their receptors in the EVs of moderate AD patients. miR-146a-5p and several other miRNAs obtained from the EVs of severe AD patients had significantly low levels compared to HC.

**Summary/Conclusion:** The neural and endothelial damage severity as reflected by AD patients’ EVs (antigen profiles cytokine and miRNA) may serve as a biomarker for disease dynamics.

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**Proteomic and transcriptomic profiling of extracellular vesicles isolated from immune-stimulated human primary astrocytes**

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**Introduction:** Astrocytes are abundant glial cells in the central nervous system that provide supportive neuronal functions. They have critical roles in regulating