Immune-proteo-metabolomic changes link to Aβ and tau pathology in Alzheimer disease

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INTRODUCTION: Tryptophan metabolism is increasingly implicated in Alzheimer's disease (AD), particularly through catabolites acting as aryl hydrocarbon receptor (AhR) ligands that influence neuroinflammation. However, their relationships with core AD pathology-amyloid-β (A) and tau (T) deposition-and associated immune-proteomic alterations remain unclear.

METHODS: We performed integrative multi-omics/high-dimensional profiling of cerebrospinal fluid (CSF) and peripheral blood from A-T- (n=19) and A+T+ (n=35) individuals using targeted metabolomics, mass cytometry, and NULISA-based proteomics, alongside inter-compartmental correlation analysis. Brain-derived tryptophan catabolism was investigated using single-nucleus RNA sequencing (snRNA-seq).

RESULTS: Thirteen differentially expressed CSF proteins in A+T+ individuals correlated positively with tryptophan metabolites and pyroglutamate, and negatively with regulatory T cells, isobutyrate and dendritic cells. Similar patterns were observed in blood. snRNA-seq suggested partial brain origin of metabolites.

DISCUSSION: Our findings highlight conserved immune-metabolic-proteomic signatures in AD and implicate tryptophan metabolism as a cross-compartmental factor relevant for biomarker and therapeutic development.