

IDENTIFICATION OF CTSK AND ACP5 IN MICROGLIA: AN OSTEOCLASTOGENIC TARGET FOR NEUROPROTECTION IN ALZHEIMER'S DISEASE

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INTRODUCTION

Severe periodontitis and Alzheimer's Disease (AD) share a chronic inflammatory etiology, yet the precise molecular effectors bridging peripheral bone resorption to central neurodegeneration remain elusive. In skeletal tissue, matrix degradation is executed by osteoclasts secreting Cathepsin K (CTSK). This study tested the hypothesis that microglia in AD undergo transcriptomic reprogramming towards an "osteoclast-like" phenotype, ectopically reactivating this lytic enzymatic machinery to mediate synaptolysis (synaptic matrix degradation) in the hippocampus.

METHODS

We conducted a translational cross-tissue bioinformatic analysis integrating oral and neuropathological transcriptomic data. The GSE10334 dataset (NCBI GEO) of gingival tissue with periodontitis was analyzed via GEO2R to establish the pathogenic co-expression profile of CTSK/ACP5. Subsequently, we investigated the differential expression of these genes in the hippocampus of AD patients (n = 30) compared to healthy controls using the AlzData database, with corrected statistical validation. Cellular specificity was determined using single-cell RNA sequencing (scRNA-seq) data from the Human Protein Atlas. Protein-protein interaction (PPI) networks were constructed in STRING-DB to map the regulation of these genes by the TREM2-TYROBP risk axis.

RESULTS

Gingival analysis confirmed CTSK and ACP5 as the primary drivers of tissue destruction in periodontitis (LogFC > 4.5, p<0.001). Crucially, probing the AD hippocampus revealed an anomalous and significant upregulation of CTSK (LogFC > 1.5, p<0.01) and ACP5, indicating a translation of bone pathology to the brain. Single-cell mapping unequivocally demonstrated that microglia are the exclusive source of CTSK in the brain parenchyma, functionally mimicking the osteoclast. Network analysis revealed that CTSK expression is dependent on TREM2 signaling, suggesting that "Disease-Associated Microglia" (DAM) utilize bone proteases to degrade the perineuronal matrix.

CONCLUSIONS

SPP1 is crucial in AD, interacting with APP and MAPT, activating the NF-κB pathway, amplifying neuroinflammation, and exacerbating neuronal damage. Elevated SPP1 expression correlates with increased APP, MAPT, and inflammatory cytokines. Periodontal infections that raise osteopontin levels may accelerate AD progression, suggesting modulation of osteopontin and control of periodontal inflammation as promising therapeutic strategies.

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