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GLIAL SENESCENCE IN ALZHEIMER'S DISEASE

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Aims

The greatest risk factor for Alzheimer's disease (AD) is ageing. One of the major hallmarks of ageing is the accumulation of senescent cells. The aims of this study were to i) quantify senescence load in microglia, oligodendrocyte and astrocyte in *post-mortem* human brain from AD and non-disease control (NDC), ii) determine the major mechanistic driver of increased cell senescence in AD.

Methods

We employed Image Mass Cytometry to co-localise cell type markers (IBA1, OLIG2, GFAP), senescence markers (SA-βGal and p16) and β-amyloid (4G8) to detect senescence in tissues from Middle Temporal Gyrus (MTG) of 10 AD and 10 NDC. snRNA-seq was generated from Entorhinal, MTG and Somatosensory Cortex of 9 AD and 9 NDC. Senescent genesets curated from public databases were used for enrichment analysis in snRNA-seq using AUcell and dream (variancePartition). β-amyloid associated senescence signature was characterised by trajectory analysis using Monocle3.

Results

In AD, 25-35% microglia, oligodendrocyte and astrocyte were positive for SA-βGal resulting in 4 to 5-fold more senescent glia than in NDC. More than 25% microglia within 10 µm around β-amyloid plaques in AD showed expression of SA-βGal while only 3% of microglia >10 µm had associated senescence markers. Geneset enrichment showed significantly increased expression of senescence genes in AD compared to NDC and were positively correlated with greater amyloid load in all three glial cells (not in neurons)**.** Trajectories of the glial nuclei described increased expression of pathways related to replicative senescence, cellular activation and stress response in microglia and oxidative stress in oligodendroglia, and astrocyte.

Conclusions

Our results highlight the high burden of senescent glia and provide evidence for different mechanisms of senescence in microglia (both replicative and stress-induced) relative to oligodendroglia and astrocyte (stress-induced) in AD.

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