Title (max 150 characters)

Intra-cellular accumulation of Aβ and pTau in Alzheimer's disease is neuronal subtype specific and partially correlates with selective vulnerability

Abstract (max 2300 characters)

Introduction

Neurodegeneration in Alzheimer's disease (AD) selectively affects a subset of "vulnerable neurons" initially. Here we sought to define intrinsic cell characteristics and local pTau and β-amyloid (Aβ) pathology associated with vulnerable neurons with the long-term objective of developing cell type-specific neuroprotective therapies.

Methods and statistical analysis

I analysed 43 *post-mortem* human middle temporal gyri from non-disease controls and AD donors with either the common (*CV*) or the AD high-risk TREM2 variants (*TREM2var*; Fancy *et al.,* 2022). To distinguish neuronal subpopulations, define their distribution and local pTau/Aβ pathology, I developed a panel of 31 antibodies for imaging mass cytometry for visualising excitatory and inhibitory neurons, glial cells, Aβ and pTau. The SIMPLI pipeline (Bortolomeazzi *et al.,* 2022) was used for image processing and analysis. Statistical analysis was performed using Dirichlet model for testing variation in cell proportions and Kruskal-Wallis plus Wilcoxon tests or ANOVA plus Tukey tests for paired group analysis of non-normal or normal distributed data, respectively. All *p* values were corrected for multiple testing.

Results

While extracellular Aβ (representing plaques) increases 2.5x in Alz*CV* and 3.5x in Alz*TREM2var* compared to their *CV* or *TREM2var* controls (p=0.01, 0.0001), intracellular signal for Aβ (intraAβ) is higher in Ctrl*CV* (13.76±5.95% intraAβ+ cells) and significantly decreases in Alz*TREM2var* cases (6.4±2.82%; p=0.0035). The neuronal subtypes accumulating intraAβ are L3-6 GAD1+ and L5-6 RORB+, which, compared to Ctrl*CV*, are selectively reduced in Alz*CV* (35.2% fewer RORB+, p=0.0002) and in Alz*TREM2var* (58.5% fewer GAD1+, p=0.045; 55.5% fewer RORB+, p=0.0000). Conversely, pTau accumulated mostly in L3 RORB+ neurons, which increased in Alz*CV* and Alz*TREM2var* samples compared to non-disease controls (23.9% more, p=0.02; 44.5% more, p=0.02).

Conclusions

My results indicate RORB+ and GAD1+ neurons are vulnerable in AD and that pathological intraAβ accumulation, rather than pTau, may be initiating early neurodegeneration. I will next explore which Aβ fragment accumulates in vulnerable neurons and its relation to defective autophagy, as well as the proximity of vulnerable neurons to activated glia.