Alzheimer's Association International Conference

P3-032 - Glial and neuronal mechanisms contributing to differential risks in *TREM2 R47H* and *R62H* variants in Alzheimer's Disease

Tuesday, July 18, 2023
7:45 AM - 3:15 PM

Theme

Basic Science and Pathogenesis

Abstract

Background: Coding variants in the microglial *TREM2* ectodomain differentially (*R47H*> *R62H*) increase the risk of Alzheimer's disease (AD). To define mechanisms responsible in glia and neurons, we aimed to characterise neuropathology and transcriptomic responses in heterozygotes for these *TREM2* variant alleles and for common allele homozygotes (*CV*) in non-diseased (*n*=16) and AD (*n*=42) brain cortical tissue from 58 donors.

Method: Using immunohistochemistry (IHC) and imaging mass cytometry (IMC), we characterised neocortical b-amyloid and AT8/PHF1 pTau pathology with *CV* (*n*=30) and the *R47H* (*n*=11) or *R62H* (*n*=17) *TREM2* carriers. We performed single nuclear RNA sequencing to test for the differential gene expression (DGE) in *TREM2* and *CV* cortical tissues with greater $4G8^{+}$ b-amyloid- or $PHF1^{+}$ pTau-immunostaining.

Result: There was a two-fold increase in 4G8+, a three-fold reduction in AT8+ but no change in PHF1+ immunostaining with AD in both variants versus *CV*. We found a reduced expression of genes associated with *TREM2* function in *R47H* carriers relative to *CV* however enhanced microglial activation in *R62H* carriers. This was associated with an up-regulation of pathways such as 'neuroinflammation signalling pathway' in *R62H* not seen in *R47H*. *CV* astrocytes had little DGE with increasing pathology however both variants (*R47H*>*R62H*) had an increased proportion of differentially expressed genes suggestive of a heightened activation state. *R47H* and *R62H* astrocytes impacted pathways had opposing actions such as 'synaptogenesis signalling pathway' and 'PDGF signalling' pathways downregulated in *R47H* but upregulated in *R62H*. Neuronal gene expression changes were evident in all variants, however greatly enhanced in *R47H* in response to $4G8^{+}$ b-amyloid. With increasing $PHF1^{+}$ pTau gene expression changes were mainly seen in *R47H*. Excitatory and inhibitory neurons both exhibited DGE in *R47H* carriers and impacted pathways centred around those involved in 'synaptogenesis signalling pathway', 'SNARE signalling pathway' and 'synaptic long term depression'.

Conclusion: This analysis identified novel disease-associated transcriptomic differences in the glial response to *TREM2* and the secondary neuronal responses that can explain differences in the genetic AD risk conferred by these two *TREM2* risk variants.

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