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NEURODEGENERATIVE DISEASE

Gene expression in aged microglia is related to neurodegenerative disease

The gene expression profile of microglia from aged human brains confirms that these cells have an age-related phenotype involved in neurodegenerative disease, a new study has shown. Genes that are enriched in the profile include those associated with Alzheimer disease (AD) and multiple sclerosis (MS), and the profile is altered in carriers of the *APOE*ε2* allele.

Previous studies have implicated microglia in the pathogenesis of various neurodegenerative diseases, including AD, Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS). However, knowledge of their role is limited by an incomplete understanding of how microglial phenotype and function in humans are affected by age, the biggest risk factor for neurodegenerative disease.

"In our study, we set out to characterize the phenotype of microglia in the aged human brain as a first step towards understanding their contribution to neurodegenerative diseases," explains Elizabeth Bradshaw, who led the new work along with Philip De Jager.

> "the HuMi_Aged gene set was enriched with susceptibility genes for AD and MS"

The researchers used techniques developed in their laboratory to isolate microglia from post-mortem brains from participants of the ROSMAP study of ageing and AD (run by David Bennett at Rush University) and construct RNA-seq libraries from a relatively small number of cells. "Our approach is novel, as it allows autopsy specimens to be transported from sites across the USA, allows isolation of other cell types along with microglia, and works well with cell numbers that are a fraction of what other current protocols require," says De Jager.

Samples analysed were from ten individuals with a mean age of 95 years and amyloid and tau pathology typical for this age — three individuals had been diagnosed with AD. Comparison with genes previously identified as being preferentially expressed by microglia showed that 1,054 genes — dubbed the HuMi_Aged gene set — were enriched in the aged microglia. Genes in the HuMi_Aged gene set were related to DNA damage, telomere maintenance and phagocytosis. "Contrary to general belief, there were no signs of overt, large-scale pro-inflammatory activation of microglia in the aged human brain," explains Bradshaw.

Furthermore, the HuMi_Aged gene set was enriched with susceptibility genes for AD and MS but not for PD or ALS, suggesting that the level at which susceptibility genes exert their effect through microglia varies between neurodegenerative diseases. Comparison of the gene expression profile of aged microglia with a previously published profile of microglia from middle-aged humans demonstrated that ageing results in both loss-of-function and gain-of-function changes in microglia phenotype.

The findings, says first author Marta Olah, suggest that the role of microglia in ageing is more nuanced than previously thought and requires further detailed investigation, but the HuMi_Aged gene set has already provided valuable insight. "We found the gene set to be more robustly expressed in women than in men, enriching an emerging narrative of sex-specific effects in microglia," she explains. "In addition, expression of the HuMi_Aged gene set is diminished in individuals with the protective *APOE*ε2* haplotype, suggesting a mechanism for this protective factor in AD."

The team now plan to use the same approach to look into the contribution of microglia to the pathogenesis of neurodegenerative diseases, particularly AD, PD, MS and ALS, and to investigate the effects of specific disease risk loci on microglial function. "These studies, which are currently underway in our laboratory, will enable us to identify possible commonalities between neurodegenerative diseases, novel therapeutic targets and candidates for new PET tracer ligands that could aid with tracking of disease progression and/or serve as an in vivo diagnostic tool," concludes Bradshaw.

Ian Fyfe

ORIGINAL ARTICLE Olah, M. et al. A transcriptomic atlas of aged human microglia. *Nat. Comm.* **9**, 539 (2018)