NEURODEGENERATIVE DISEASE

Microglia gone wild

Yang, H.S., Onos, K.D. et al. *Cell Rep.* **34**, 108739 (2021)

Genetic and genome-wide association studies have implicated microglia – the brain-resident macrophages – in Alzheimer's disease (AD), but their exact role in AD pathogenesis is still debated. Challenges to our understanding include the lack of models that recapitulate all aspects of human disease and differences between rodent and human microglia.

Most AD studies in mice use inbred laboratory strains, such as C57BL/6 (B6). Contrary to the human population, these strains are genetically uniform, which could contribute to the differences in microglial subsets reported between species. In a new study, Gareth Howell and his team at the Jackson Laboratory compared microglia of B6 mice to those of wild-derived mice to understand how genetic variation can influence microglial diversity. By revealing differences in microglial subtypes or states across strains, both in wild-type mice and in the context of AD mutations, the study suggests that greater genetic diversity in rodent models of AD could improve

human disease modeling and increase our understanding of cellular responses in AD.

“As the wild-derived strains CAST/EiJ (CAST), WSB/EiJ (WSB), and PWK/PhJ (PWK) were captured from the wild from different geographical regions for laboratory use, their genomes are closer to recapitulating the diversity of genetic variants that would exist in the natural world,” explain the investigators in their report.

In a previous study, the team had shown that wild-derived AD models – created by backcrossing for at least six generations the *APP/PS1* transgenes from B6 to the CAST, WSB and PWK strains – exhibited robust functional and neuropathological differences across strains. Bulk RNA sequencing also showed that microglial gene expression varied across the strains.

Here, the investigators took the transcriptomic analysis a step further and performed single-cell RNA-sequencing on microglia isolated from female B6.*APP/PS1*, CAST.*APP/PS1*, PWK.*APP/PS1*, WSB.*APP/PS1* mice and their wild-type

controls. They annotated the different microglia clusters (including homeostatic microglia, disease-associated microglia, activated-response microglia and interferon-responding microglia) and compared the percentage of cells and gene enrichment in each cluster. Their analysis revealed important strain-, genotype-, and strain-by-genotype- specific changes in the abundance of microglia subtypes and microglial gene expression.

The investigators conclude that the changes in microglia associated with natural genetic variation are predicted to impact microglia biology and produce different neuroimmune environments in healthy and diseased states. “This wild-derived AD panel offers a level of genetic and phenotypic diversity that can aid in determining the role of microglia in human AD,” they write.

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