Nature Reviews Neuroscience | Published online 29 Jun 2017; doi:10.1038/nrn.2017.83

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A protective population?

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Whether immune cells contribute to or mitigate disease progression in neurodegenerative disorders remains unclear. In a new study, Keren-Shaul *et al.* have used single-cell gene expression profiling to characterize the involvement of immune cells in a mouse model of Alzheimer disease (AD), revealing the existence of a specific population of microglia that are activated through a two-step process and have the potential to influence AD pathology.

Many previous analyses of microglial contributions to neurodegeneration have relied on the detection of microglia-specific cell surface markers; however, the increasing evidence for microglial heterogeneity suggests that it will be important to identify and understand the activity and roles of the distinct subsets of microglia, as well as to avoid potential contamination by other immune cells. Keren-Shaul *et al.* therefore performed single-cell RNA-sequencing on immune cells isolated from the brains of mice that expressed five human familial AD mutations (5XFAD mice) and from wild-type controls, revealing the presence of three subpopulations of microglia with distinct gene expression profiles: a large group that the authors termed 'homeostatic microglia' and two smaller groups found exclusively in the 5XFAD mice that the authors collectively named 'disease-associated microglia' (DAM).

Compared with homeostatic microglia, DAM showed altered expression of several groups of genes associated with the regulation of microglial function, several of which (including triggering receptor expressed on myeloid cells 2 (*Trem2*), lipoprotein lipase (*Lpl*) and apolipoprotein E (*Apoe*)) are also associated with increased AD risk in humans. Further analysis revealed that, in the brains of 5XFAD mice, microglia changed 'state' (in terms of their gene expression profile) as disease pathology progressed; that is, homeostatic microglia were replaced by an intermediate state — in which 'checkpoint' genes that are known to restrain the immune activity of microglia were downregulated — and finally became fully activated DAM.

Which factors mediated this transition? The expression of *Trem2* has previously been associated with both microglia function and AD risk. The authors showed that, in 5XFAD mice with a *Trem2* knockout, there was a greater abundance of 'intermediate microglia' but no DAM. This suggests that the initial triggering of DAM activation and downregulation of checkpoint genes do not require TREM2 but that signalling by this receptor is important to upregulate the phagocytic and lipid metabolism pathways.

Phagocytosis of amyloid-β, which accumulates in plaques in the brains of individuals with AD, has been suggested to be one way in which microglia could influence AD progression. The authors examined the possible role of DAM in this process by conducting immunostaining, *in situ* hybridization and histological staining in brain tissue samples of 5XFAD mice and from individuals with AD. They showed that DAM are located close to plaques and that many contained particles of amyloid-β, indicating that phagocytosis had taken place.

These findings show that AD progression, in a mouse model, leads to a sequential transformation of a subpopulation of microglia from homeostatic into phagocytic cells (DAM) and suggest that a similar process may take place in human AD. It further suggests that under certain circumstances — such as a particular genetic background or during ageing — appearance of these cells might occur too late or in insufficient numbers to combat the disease.

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ORIGINAL ARTICLE Keren-Shaul, H. *et al.* A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* http://dx.doi.org/10.1016/j.cell.2017.05.018 (2017)
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