Alzheimer's disease

T cells make a home in the degenerating brain

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A subpopulation of adaptive immune cells patrols the brain and cerebrospinal fluid in people who have Alzheimer's disease. This discovery should broaden our understanding of how the immune system can influence neurodegeneration. See p.399

For decades, research into Alzheimer's disease has centred on neurons. Only in the past few years have scientists identified a role for immune cells in the progression of this neurodegenerative disorder[1]. Most research has focused on the nonspecific, innate branch of the immune system. But Gate *et al.*[2] report on page 399 that an immune-cell subpopulation belonging to the adaptive immune system – which remembers and responds to specific foreign invaders – might also have a role in Alzheimer's disease.

The authors isolated and analysed immune cells from the blood of healthy people and people who had Alzheimer's disease or a precursor of the disease known as mild cognitive impairment (MCI). They discovered an immune-cell subpopulation called $CD8^+$ T effector memory $CD45RA^+$ (T_{EMRA}) cells that was associated with MCI and Alzheimer's disease. T_{EMRA} cells have previously been linked to immunological memory, and they release inflammatory and cytotoxic (cell-death-promoting) molecules[3].

Analysis of a separate cohort of people who had Alzheimer's disease revealed that an increased presence of T_{EMRA} cells in the blood was associated with compromised cognitive performance. This finding could indicate that T_{EMRA} cells contribute to neuronal dysfunction by secreting inflammatory and cytotoxic molecules in the brain (Fig. 1). Alternatively, a damaging mechanism that causes cognitive dysfunction might also elicit an inflammatory T_{EMRA}-cell response in the blood.

Gate *et al.* corroborated their findings *in vitro*, showing that stimulation with an inflammatory molecule caused immune cells from people who had MCI or Alzheimer's disease to release more interferon-γ (a key pro-inflammatory protein) than did immune cells from people who did not have these conditions. This is consistent with another study[4], which demonstrated that T cells derived from people who have Alzheimer's disease become more active than do those from healthy people when exposed to β-amyloid, a protein associated with this disorder.

The authors then asked whether the presence of T_{EMRA} cells could be used to predict disease status. Indeed, a machine-learning algorithm could use measurements of T_{EMRA} cells (together with information about other immune-cell populations) to distinguish between healthy people and those with MCI or Alzheimer's disease with about 80% accuracy. Many immune processes alter during ageing and so are of limited use for predictive clinical testing, but age did not influence the level of T_{EMRA} cells. This type of technique, once refined, might therefore be used alongside biomarkers of neuronal damage and degeneration for blood-based diagnostic tests, improving our ability to detect Alzheimer's disease at an early stage.

> **"This is perhaps the first evidence that clonally expanded T cells invade the cerebrospinal fluid in age-related neurodegenerative diseases."**

Next, Gate and colleagues analysed the brains of people who had died with Alzheimer's disease. This revealed $CD8^+$ T cells (which might be T_{EMRA} cells) in the perivascular space around the brain's blood vessels, and at sites of β-amyloid deposition, as previously reported for T cells in Alzheimer's disease[5,6]. $CD8^+$ T cells are known to physically contact and sever neuronal processes, causing structures called neuritic spheroids to form nearby – another hallmark of Alzheimer's disease[7]. Thus, it is conceivable that T_{EMRA} cells contribute to neuronal damage not only by secreting immune molecules, but also by directly damaging neuronal processes[7].

MCI and Alzheimer's disease are associated with changes in the number and proportion of T cells in the cerebrospinal fluid (CSF) that surrounds the brain and spinal cord[8,9]. The investigators therefore asked whether T_{EMRA} cells were found in the CSF and whether there was evidence of 'clonal expansion' of this cellular subpopulation. Naive T cells each have different T cell receptor (TCR) proteins, but when the receptor is stimulated by a particle called an antigen, the cell proliferates to form clones of itself. The presence of more than one cell with the same TCR therefore indicates clonal expansion – a sign that T cells have been activated previously. The authors sequenced TCRs from an independent cohort of people and identified several T-cell clones, including

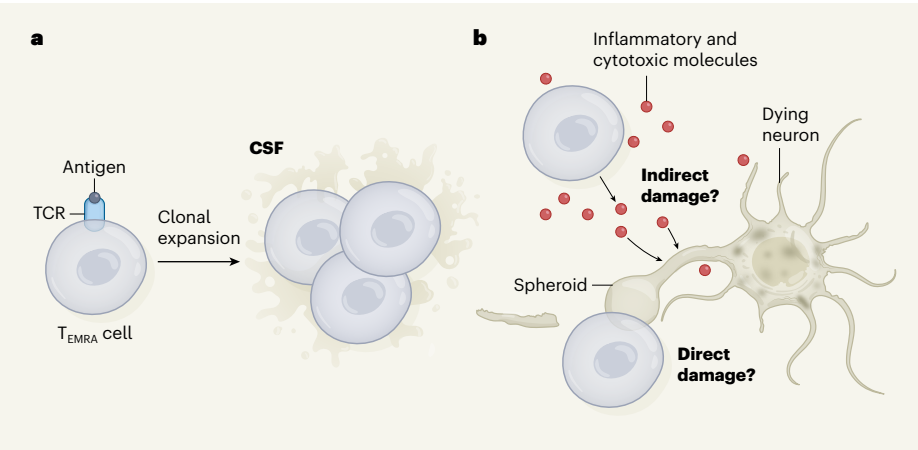

Figure 1 | T_{EMRA} cells and age-related neurodegeneration. Gate *et al.*[2] report that the presence of immune cells called $CD8^+$ T effector memory $CD45RA^+$ (T_{EMRA}) cells in the brain is associated with Alzheimer's disease. **a**, Evidence from a few people suggests that the cells are activated by binding between the T-cell receptor (TCR) and an antigen molecule (which can be from a host cell or a foreign invader). The cells then proliferate to produce an expanded pool of T_{EMRA}-cell clones. The cells patrol the cerebrospinal fluid (CSF). **b**, T_{EMRA} cells might promote neuronal damage indirectly, by releasing inflammatory and cytotoxic (death-promoting) molecules, or directly, by physically interacting with and severing neuronal processes, causing the formation of structures called spheroids that are associated with Alzheimer's disease. Alternatively, they might have no role in disease progression (not shown).

T_{EMRA} cells, in people with Alzheimer's disease. This is perhaps the first evidence that clonally expanded T cells invade the CSF in age-related neurodegenerative diseases.

Gate *et al.* then validated their result using gene-expression analysis. This revealed that the T_{EMRA}-cell population was the predominantly expanded T-cell clone in each person who had Alzheimer's disease. The population expressed various cytotoxic genes, and was enriched in the hippocampus — a brain region crucial for human memory. In line with this observation, hippocampal T-cell infiltration promotes cognitive decline in a mouse model of Alzheimer's disease[10]. The authors also found evidence for T_{EMRA}-cell clones and gene-expression changes in the CSF of people who had another neurodegenerative disorder, Parkinson's disease, highlighting the possibility that different age-related neurodegenerative diseases share similar molecular underpinnings.

Which antigens drive clonal expansion of T_{EMRA} cells? By comparing TCR sequences from people who had MCI and Alzheimer's disease, the investigators found evidence that clonally expanded T_{EMRA} cells had been bound by two antigens produced by a virus of the herpes family, Epstein–Barr virus (EBV). However, it is important to note that a role for EBV infection in neurodegeneration has not yet been reported, and Gate *et al.* make no suggestion that EBV is involved in the development of Alzheimer's disease.

Gate and colleagues' data involve only a few patients and should be interpreted with great care, particularly given that EBV infects about 95% of people during early life[11]. Previous work[12] has shown a complex relationship between herpes viruses and Alzheimer's disease in mice. One the one hand, β-amyloid fibres can entrap herpes viruses, extending survival in mouse models of Alzheimer's disease. But on the other hand, virus infection strongly increases β-amyloid deposition in these animals.

In addition, a study[11] of 85 people who had Alzheimer's disease found evidence of EBV DNA in the brains of only 6% of cases. All of these people carried the gene *APOE4*, which is associated with a high risk of Alzheimer's disease and could explain why they developed the disorder. The same study did find that antibody responses against EBV increased during cognitive deterioration and progression of Alzheimer's disease[11]. However, these responses are quite common in older people. Moreover, a recent meta-analysis found no correlation between herpes-virus infection and dementia[13]. Longitudinal studies involving many more people will be needed before solid conclusions can be drawn.

It will be interesting to reconcile Gate and colleagues' data with the finding[14] that T cells can restrain cognitive deficits in mouse models of Alzheimer's disease. Analysis of less-prominent T-cell clones in people with and without disease might reveal other, potentially harmful — or even protective — subclones. In addition, the current study will no doubt renew efforts to define the cross-talk between innate and adaptive immunity in general, as well as in neurodegeneration. Perhaps, in the future, these interactions could be harnessed for diagnostic purposes or to develop therapeutic interventions.

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Cardiovascular biology

Platelets have a hold over immune cells

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Plaques are lipid-rich structures in the blood-vessel wall that can cause heart attacks or strokes if they rupture. It now seems that blood-cell fragments called platelets alter the function of immune cells in ways that accelerate plaque formation.

Heart attacks or strokes might seem to be sudden events, but they are the consequences of a condition called atherosclerosis, which can be decades in the making. Atherosclerosis involves the accumulation of lipids and immune cells into structures called plaques in the blood-vessel wall. If these plaques become unstable they can rupture, blocking blood flow and so depriving tissues such as the heart and brain of oxygen, respectively triggering a heart attack or a stroke. Identifying precisely how plaques grow at cellular and molecular scales is therefore crucial for understanding and so treating atherosclerosis. Writing in *Science Translational Medicine*, Barrett *et al.*[1] enrich our thinking about how atherosclerosis evolves, providing evidence that platelets in the blood promote the formation of bigger, more dangerous plaques by shaping the function of immune cells.

Monocytes are a class of short-lived immune cell crucial to host defence. They survey their environment, patrolling the vasculature and frequently migrating in and out of the blood to scout for injuries or infections. This movement is aided by endothelial cells, which demarcate the border between blood and tissue, and which produce a panoply of monocyte-attracting chemical messengers, enabling monocyte surveillance of and migration across the blood-vessel wall. Platelets — blood-cell fragments best known for making blood clots — likewise help monocytes to infiltrate the vessel wall by adhering to the cells to form monocyte–platelet aggregates. Precisely how such aggregates promote migration is not clear, but it is known that platelets can deliver a variety of mediators to which monocytes can respond[2].

Because of their role in monitoring the vasculature, monocytes are key to the development of atherosclerosis. Voracious eaters, they ingest lipids that accrue in plaques, before morphing into larger, less agile macrophages. As this transformation occurs, the cells can wreak inflammatory havoc, contributing to a feed-forward loop that generates bigger, rupture-prone plaques[3]. But because monocytes are crucial for host defence, eliminating them entirely is not therapeutically viable. Identifying and blocking factors involved in monocyte recruitment to plaques might, however, be an alternative strategy.

Barrett and colleagues investigated interactions between platelets, monocytes and their descendent macrophages in mice that have abnormally high levels of cholesterol — a risk factor for atherosclerosis. They observed that platelets adhere to monocytes in blood more readily when mice have high cholesterol levels, bolstering the idea that monocyte–platelet