millennium BC (11,000–12,000 years ago) alongside those of the chickpea[9]. However, the broad bean is one of very few crops for which no sexually compatible wild relative is known. Despite extensive efforts to cross the broad bean with other species of the genus *Vicia*, no successful crosses have been achieved.

It has been speculated that the immediate wild relative of the broad bean might be extinct, lost during approximately 10,000 years of agricultural expansion. It is also possible that the wild relative is not extinct but not yet discovered, perhaps existing in a remote region, such as the Pamir Mountains of Central Asia, from which few geneticists have been able to collect wild relatives of crops. The broad-bean genome will now allow researchers to examine a third hypothesis — that the ancestor of cultivated broad beans underwent major chromosomal rearrangements during domestication, altering it enough to sexually isolate it from its wild relatives.

The broad bean is part of a subgroup of legumes in the genus *Vicia* and the broader tribe Viciaea, whose genome sizes are substantially bigger than those of other legumes. Other members of this subgroup, such as field peas (*Pisum sativum,* 4.45 Gb), lentils (*Lens culinaris,* 4 Gb) and grass peas (*Lathyrus sativus*, 6.3 Gb), harbour many transposable elements that explain this relative increase — these repetitive DNA sequences jump around the genome, propagating as they go[5]. Similarly, Jayakodi *et al.* found that about 79% of the broad-bean genome was derived from transposable elements. Going forward, a better understanding of how transposable elements move might help researchers to understand the part that they play in speciation — not just in the broad bean, but also in groups such as lentils, in which this kind of genetic variation is common.

It is to be hoped that the increasing cost-effectiveness of long-read DNA sequencing will soon support the development of a genus-level pangenome (a collection of sequences that represents the diversity of the genus) for *Vicia*, or even a broader super-pangenome[10] for this genus and other closely related crops. This type of resource will help to illuminate the evolution of this group and its members' genomes. Understanding this variation will help breeders to harness genome regions in distantly related wild species that confer disease resistance and climate resilience, and will facilitate the sharing of genomic information between legumes.

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Alzheimer's disease

Activated immune cells drive neurodegeneration

Ian H. Guldner & Tony Wyss-Coray

An analysis of mice carrying the protein tau — a hallmark of Alzheimer's disease — reveals that immune cells collaborate to drive tau-mediated neurodegeneration, and that drugs already in use in the clinic can combat this decline. **See p.668**

Immune cells called T cells were long discounted as players in brain immunity except in rare circumstances, in part because of dogmatic ideas about their inability to penetrate the blood–brain barrier[1]. However, it has become clear in the past two decades that the adaptive immune system, of which T cells are a major part, does act in the human brain[2]. On page 668, Chen *et al.*[3] describe a role for T cells in neurodegeneration. The authors' work implies the need for a revised view of adaptive immunity in the brain.

Alzheimer's disease is characterized by the accumulation in the brain of extracellular amyloid-β (Aβ) protein and intracellular aggregates of tau protein. But although these proteins are both considered hallmarks of the disease, brain atrophy correlates highly only with tau accumulation, not with Aβ deposition[4]. Might tau trigger a specific response in surrounding cells that drives atrophy? Chen and colleagues address this question directly by using mice that have Aβ deposition or tau aggregation (known as tauopathy), but not both.

There is mounting evidence for an inflammatory immune response in mouse models of neurodegeneration[5] and in people who have Alzheimer's disease[6]. The authors therefore focused on immune cells as possible drivers of tau-specific neurodegeneration. They isolated immune cells from the brains of mice with Aβ deposition and from tauopathy mice, and analysed the cells using single-cell RNA sequencing — an unbiased way to identify cell types on the basis of the genes they express. The analysis revealed 12 immune-cell populations in both models, with many more T cells in the brains of the tauopathy mice than in those of mice with Aβ deposition.

Chen *et al.* validated this finding by examining slices of brain from mice and from people who had died with Alzheimer's disease. Tissue staining revealed that T cells had accumulated in the hippocampus and entorhinal cortex of tauopathy mice and in the superior frontal gyrus in humans. These regions are involved in learning and memory, and are hotspots for tau accumulation. This distribution suggests that T cells respond to tau, and might induce neuronal damage that contributes to the cognitive defects associated with Alzheimer's.

There are many types of T cell, from $CD8^+$ T cells that kill cells flagged by the immune system, to regulatory T cells that suppress immune responses. Knowledge of the subtype and state of T cells is therefore key to determining their potential role in brain atrophy. Examining their sequencing data, the authors discovered that tauopathy mice carried more of a potentially harmful subtype of T cell — activated $CD8^+$ effector T cells — than did mice with Aβ deposition. With increasing amounts of tau in the brain, these cells began to show signs of exhaustion, a dysfunctional condition in which T cells that have been chronically activated lose their normal abilities. The data also revealed that the T cells were clones of a single parent, suggesting that the cell had proliferated (a sign of activation) in response to a specific factor.

T cells are activated when their receptor binds to an antigen (a non-self protein fragment, or a modified self protein fragment)

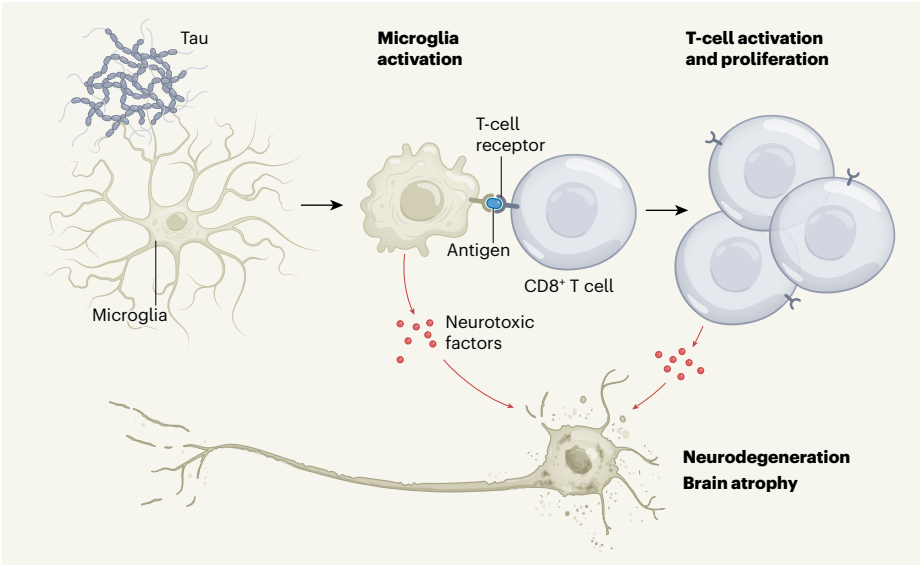

Figure 1 | A role for immune cells in tau-specific neurodegeneration. Chen *et al.*[3] examined mice that harboured aggregates of the protein tau, which is associated with Alzheimer's disease. They found that brain-specific immune cells called microglia adopt an activated, disease-associated state in these animals. The authors provide evidence that an antigen (of unknown identity) is presented by microglia to immune cells called $CD8^+$ T cells, activating the T cells and so causing their proliferation. They propose that the microglia and activated T cells release unknown 'neurotoxic' factors that kill neurons and so lead to brain atrophy.

that is presented by another cell. What cell might be presenting antigens in the tauopathy mice? Examination of the brain's resident immune cells, microglia, revealed that many microglia in these animals had adopted a disease-associated state[5], or had activated signalling pathways that trigger immune responses[7]. Crucially, these microglia expressed MHC II molecules, a key component of the antigen-presentation machinery, and were in close proximity to $CD8^+$ T cells in brain slices from tauopathy mice. Furthermore, *in vitro* experiments demonstrated that culturing microglia and T cells together with a foreign antigen resulted in T-cell proliferation.

These largely descriptive results led Chen *et al.* to hypothesize that microglia and T cells conspire to drive brain atrophy in response to tau (Fig. 1). To test this hypothesis, they gave tauopathy mice a drug or an antibody known to result in the death of microglia or T cells, respectively. If given when neurodegeneration was developing, both cell-depleting treatments led to a marked decrease in brain atrophy, and reduced signs of the harmful effects of tau. Furthermore, T-cell depletion led to near-normal performance in various tests of memory and learning. In support of the idea that T cells and microglia interact, depletion of microglia reduced T-cell numbers in the brain, and T-cell depletion reverted microglia to a state more like that seen in disease-free brains.

It might not be viable to deplete entire immune-cell populations in humans, but modulating the immune response could be an alternative. The researchers injected tauopathy mice with anti-PD-1 antibody, which is used clinically in cancer immunotherapy, because it causes a chain reaction resulting in T-cell activation. Short-term anti-PD-1 treatment increased the proportion of regulatory T cells, which can inhibit activated T cells, and long-term anti-PD-1 treatment reduced neurodegeneration and tau accumulation, as has been shown in other studies[8,9]. However, Chen *et al.* did not investigate how anti-PD-1 treatment affected cognition, something that would need to be established in animal models before any similar approach can be tested in people. Nevertheless, these findings provide insight into the interplay between $CD8^+$ effector T cells and immunosuppressive regulatory T cells in neurodegeneration.

Chen and colleagues' work adds to a growing body of research indicating that specialized T cells in the brain not only are essential for physiological functions[10] but also have regulatory and toxic roles in ageing and neurodegeneration[11]. However, many questions remain. For instance, are the T cells new migrants to the brain, or derived from cells that fulfil physiological roles and reside in specific brain niches? Whether T cells can be tuned to combat disease while preserving their beneficial functions in the brain needs investigation.

What is the mechanism of antigen presentation in the brain? Typically, antigen presentation and T-cell activation occur in lymph nodes in a process that involves bespoke antigen-presenting cells, but Chen *et al.* point to a role for microglia — a cell type that is less effective at antigen presentation than other cell types[12,13]. They provide mainly correlative data to support this suggestion, leaving room for uncertainty. Perhaps there is a subset or state of microglia endowed with potent antigen-presentation skills. Alternatively, specialized immune cells called macrophages, which reside at the brain's border, might help to present antigens. A third possibility is that other cells present antigens to regulatory and $CD8^+$ T cells.

What antigens are T cells recognizing in tauopathy and, more generally, during ageing and neurodegeneration? They might be viral, because T cells have been shown to recognize viral antigens in the cerebrospinal fluid of people with Alzheimer's disease[6], and large epidemiological studies broadly implicate viral antigens in neurodegeneration[14,15]. T cells can also recognize a disease-promoting protein called α-synuclein[16,17] that forms aggregates in Parkinson's disease, perhaps suggesting that the cells recognize tau itself. And T cells bind to many other types of antigen. A rapidly expanding toolset, including antigen-identification methods[18,19], should help to clarify immunological processes in the brain, transforming our understanding of brain ageing and neurodegeneration.

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