News & views

Neurodegeneration

A protective pairing in Alzheimer's disease

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In a mouse model of Alzheimer's disease, interleukin-3 protein released by cells called astrocytes activates microglia, the immune cells of the brain. These then cluster around disease-associated protein aggregates and help to clear them. **See p.701**

Immune signalling associated with inflammation is sometimes considered a thing to be avoided. However, immune signalling can also be protective, quelling damage and disease-causing microorganisms (pathogens). In the brain, multiple cell types work together to maintain brain health, mediate inflammatory responses and optimize the function of the main output cells, neurons. On page 701, McAlpine *et al.*[1] uncover a signalling axis between two of these brain cell types, astrocytes and microglia. They demonstrate that this signalling, mediated by the immune protein interleukin-3 (IL-3), limits disease progression and brain dysfunction in a model of Alzheimer's disease.

Alzheimer's disease (AD) is a devastating and prevalent neurodegenerative disorder that leads to the loss of brain cells and of the synaptic connections between neuronal cells, resulting in progressive cognitive decline. One hallmark of AD is the presence of disease-associated aggregates of different proteins in the brain: that is, plaques made up of the protein amyloid-β (Aβ), and neurofibrillary tangles made up of the protein tau[2].

Normally, astrocytes and microglia help to maintain neuronal health and function by clearing debris, recycling neurotransmitter molecules and supporting communication across synapses[3]. In the brain of a person with AD, astrocytes and microglia become activated, produce inflammatory molecules and aggregate around the protein plaques. This microglial aggregation can be protective, by preventing loose (soluble) Aβ protein from diffusing throughout the brain[4]. However, the signals that coordinate the functions of microglia are not fully understood. McAlpine *et al.* show that the astrocyte-produced cytokine IL-3 is one of these signals, and that it plays a central part in a model of AD.

Cytokines are soluble signalling proteins that are a key form of immune communication. They are involved in complex signalling loops that can initiate, intensify or resolve inflammation, recruit immune cells to where they are needed, and aid the clearance of pathogens and cellular debris. Their impact on the brain has long been of interest in neurological diseases in which inflammation is observed alongside impairments in neural function.

The roles of IL-3 in the brain have not been particularly well studied. However, it is known to regulate inflammation in multiple ways, such as by driving the proliferation of immune cells, including those that circulate in the blood[5], and it has been associated with AD risk in studies of patient plasma[6,7].

McAlpine *et al.* examined a model of AD in which mice carry five mutations that have been implicated in the disorder in humans. These AD mice develop Aβ plaques and show progressive impairments in short-term memory with age[8]. When these AD-model mice also lacked IL-3, they showed an increased accumulation of Aβ plaques, higher levels of soluble Aβ and greater impairments in short-term and spatial memory.

To pinpoint the cellular sources of IL-3 in the brain, McAlpine *et al.* generated mice in which IL-3-producing cells are fluorescently labelled; this approach identified a subset of astrocytes as a major source of IL-3. AD mice in which IL-3 was deleted specifically from astrocytes showed increased accumulation of Aβ plaques and more severely impaired short-term memory compared with AD mice. The authors observed a similar effect in AD mice that completely lacked IL-3, suggesting that astrocytes are the key cellular reservoir of the protein in this AD model (Fig. 1). Notably, the aggregation of microglia near Aβ plaques

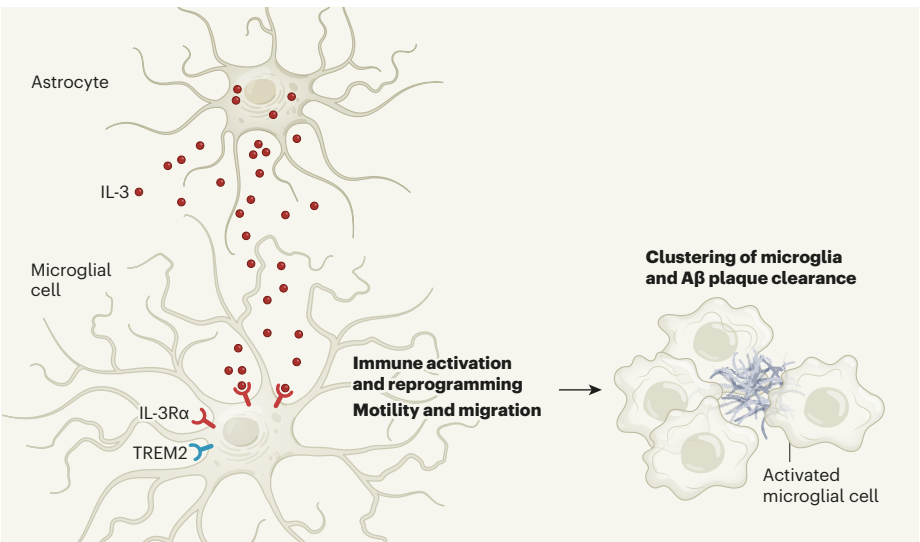

Figure 1 | Interleukin-3 (IL-3) protein signalling in the brain can help to clear disease-associated protein aggregates. McAlpine *et al.*[1] studied a mouse model of Alzheimer's disease (AD) in which disease-associated plaques consisting of amyloid-β (Aβ) protein form in the brain. The authors revealed a signalling axis between two types of brain cell, astrocytes and microglia, that had not previously been implicated in AD. Astrocytes express and release IL-3, which activates IL-3Rα on the surface of a subset of microglia that also express the cell-surface receptor TREM2. The IL-3 signal activates and reprograms the microglia, promoting their movement and clustering around Aβ plaques. Microglia have a role in clearing Aβ plaques[4] and, consistent with this, McAlpine *et al.* found that treating AD-model mice with brain injections of IL-3 resulted in reduced build-up of Aβ plaques in these animals. (Figure adapted from Extended Data Fig. 9e in ref. 1.)

was reduced in AD mice lacking astrocytic IL-3.

The authors next identified the targets of IL-3 in the brain. They found that microglia express the IL-3 receptor IL-3Rα, and that levels of this receptor are substantially increased with age and in the AD model compared with young, wild-type mice. Deleting IL-3Rα specifically from microglia in the AD mice resulted in effects on Aβ plaque burden and memory similar to those observed in AD mice lacking IL-3 in astrocytes.

Strikingly, McAlpine and colleagues found that injecting IL-3 into the brains of AD mice could reduce Aβ build-up and stimulate the clustering of microglia around Aβ plaques (Fig. 1). Continuous delivery of IL-3 into the brains of IL-3-deficient AD mice over four weeks resulted in a remarkable reduction in the size and amount of plaques and the levels of soluble Aβ, as well as improvements in short-term memory relative to results seen in AD mice injected with an inactive control substance. This is a key finding with potential therapeutic implications.

Interest in the role of microglia in AD has increased dramatically since the discovery that a variant of the gene encoding the receptor protein TREM2, which is expressed by microglia, is associated with risk for AD[9]. McAlpine *et al.* show that *Il3ra* is enriched in a previously described subset of 'disease-associated microglia' that are activated through the TREM2 receptor[10]. Moreover, the authors found that deletion of *Trem2* prevented the increase in microglial expression of IL-3Rα in their AD model, raising the question of whether *TREM2* mutations associated with AD risk in humans might prevent this protective IL-3-dependent response.

Indeed, the authors also found evidence that this pathway is at work in the human brain. In brain tissue from individuals who had died with AD, the authors observed astrocyte expression of IL-3 and higher microglial expression of IL-3Rα than in the brains of age-matched individuals without AD. Moreover, the amount of microglial IL-3Rα expression correlated with the length of time for which these individuals had been diagnosed with AD, as well as with the accumulation of Aβ plaques.

How does IL-3 promote the protective functions of microglia? The authors found that in AD mice lacking IL-3, microglia did not cluster around plaques, and plaque deposition was greater than in AD mice. In experiments with human microglia in culture, treating these cells with IL-3 promoted migration towards AD-associated protein aggregates.

It is important to keep in mind that IL-3 might offer protection through more than one mechanism. For example, IL-3 was particularly abundant in astrocytes at the blood–brain barrier, which controls the passage of proteins and cells from the circulatory system to the brain. Populations of immune cells called macrophages, which reside at the brain's borders, might have been targeted by some of the genetic tools used to manipulate IL-3Rα expression. Such cells could also be affected by IL-3 to alter the entry of molecules or cells into the brain. Although McAlpine *et al.* examined some aspects of the integrity of the blood–brain barrier and found it to be intact, other unmeasured variables such as active transport of blood-borne molecules to the brain could be affected[11].

In addition, it is possible that other brain cell types could express the IL-3 receptor in some contexts and respond to IL-3. Further dissecting the impact of IL-3 signalling on other cellular players will be a crucial next step.

Nonetheless, these findings are an exciting advance in understanding the role of astrocytes and microglia in AD, a disease that is notoriously difficult to treat and that currently lacks any curative or restorative therapies. Although caution should be exercised in translating these findings to the clinic, particularly given the role of IL-3 and IL-3Rα in certain autoimmune disorders[12], this study raises the intriguing idea that IL-3 or related molecules could have therapeutic potential in AD. Could this be one step towards personalized therapy for individuals with AD who carry a risk-associated *TREM2* variant? Further defining the roles of IL-3 in health and disease will be essential to fulfil the promise of McAlpine and colleagues' findings.

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Organic chemistry

Boron groups installed directly into molecules

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Compounds called borylated azines have untapped potential for organic synthesis, but have faced problems associated with their preparation, stability and reactivity. A new class of these compounds provides a solution. **See p.677**

The search for new pharmaceutical drugs by medicinal chemists relies on the synthesis of diverse compound libraries for biological testing. Of the reactions used for this purpose, those involving boron-containing organic molecules (known as organoboron compounds) are among the most popular because of the commercial availability and wide reactivity of these reagents[1]. On page 677, Kim *et al.*[2] report a method for the synthesis of organoboron compounds called borylated azines. The authors demonstrate that these compounds can participate in reactions common to other organoboron compounds, but offer distinct advantages, such as ease of preparation and impressive stability. Importantly, these reagents will allow a full exploration of the therapeutic potential of molecules that have previously been difficult to prepare.

Azines are nitrogen-containing analogues of benzene rings and are present in many of the top-selling pharmaceuticals approved by the US Food and Drug Administration (see go.nature.com/2dirpwf). These medicines target several disease areas, including arthritis, diabetes and several types of cancer. If a boron-containing group is attached to an azine, the resulting borylated azine can be used as a reagent for the synthesis of many different azine-containing molecules — a crucial process for diversifying compound libraries. Kim *et al.* explored the use of transformations called C–H functionalization reactions to prepare borylated azines.

Although once regarded as an academic curiosity, C–H functionalization reactions are now a powerful methodology in organic synthesis. In these processes, a carbon–hydrogen