Title
A protective signal between the brain’s supporting cells in Alzheimer’s disease

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[Strapline (one or two words to describe the general field):] Neurodegeneration ***[Suggested strapline OK?]***

Print: A protective pairing in the Alzheimer's brain

Online: A protective signal between the brain's supporting cells in Alzheimer's disease

Jerika J. Barron and Anna V. Molofsky

Standfirst: In a mouse model of Alzheimer's disease, interleukin-3 protein released by cells called astrocytes activate the immune cells of the brain, microglia, which then cluster around and help to clear disease-associated protein aggregates. See p.XXX

Inflammation is sometimes considered a thing to be avoided. However, immune signaling is also protective, quelling damage and disease-causing microorganisms (pathogens). In the brain, multiple cell types work together to maintain brain health, to mediate inflammatory responses, and to optimize the function of the main output cells: neurons. Here, McAlpine *et al.*[1] uncover a signaling axis between two of these brain cell types, astrocytes and microglia. They demonstrate that this signaling, 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 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: 'plaques' consisting of the protein amyloid-β (Aβ), and so-called neurofibrillary tangles made up of tau protein[2].

Normally, astrocytes and microglia help to maintain neuronal health and function by clearing debris, recycling neurotransmitter molecules and supporting the 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 may be protective, by preventing loose (soluble) protein from diffusing throughout the brain[4]. However, the signals that coordinate their functions 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 role in a model of AD.

Cytokines are soluble signaling proteins that are a key form of immune communication. They are involved in complex signaling loops that can ramp up or resolve inflammation, recruit immune cells to where they are needed, and initiate the clearing 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.

In the brain, IL-3 is not a particularly well-studied cytokine. 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.

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. However, when these AD model mice also lacked IL-3, they showed an increased plaque burden, more soluble Aβ, as well as 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 plaque burden and more severely impaired short-term memory compared with AD mice. This result was similar to findings in AD mice that completely lacked IL-3, suggesting that astrocytes are the key cellular reservoir of this protein in this AD model. Notably, the aggregation of microglia near Aβ plaques was reduced in AD mice lacking astrocytic IL-3, compared with what was observed in AD mice

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. The effects of deleting IL-3Rα specifically from microglia in the AD mice on Aβ plaque burden and memory were 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 burden and stimulate the clustering of microglia around Aβ plaques. ***[OK? I removed the part about 'in AD mice deficient for IL-3' because it looks like the injections were only done in the 5xFAD mice, not the Il3$^{-/-}$ 5xFAD mice. Please check; apologies if I have misunderstood this.]*** Continuous delivery of IL-3 into the brains of IL-3 deficient AD mice over 4 weeks resulted in a remarkable reduction in the size and amount of plaques as well as the amount of soluble Aβ), and improvements in short-term memory relative to 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 dramatically increased since the discovery that a variant of the gene encoding the receptor protein TREM2 is associated with risk for AD[6]. McAlpine *et al.* show that *Il3ra* is enriched in a previously described subset of 'disease associated microglia' that are activated via the TREM2 receptor[7]. McAlpine *et al.* 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 ***[OK?]*** might prevent this protective IL-3-dependent response.

Indeed, the authors also found evidence that this pathway is at play in the human brain. In brain tissue from individuals who 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 controls without AD. Moreover, expression of IL-3Rα by microglia in the brains of individuals with AD correlated with the length of time these individuals had been diagnosed with AD, as well as with Aβ burden.

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 burden was worse compared to 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 IL-3 may protect through more than one mechanism. For example, IL-3 was particularly abundant in astrocytes at the blood-brain barrier, a series of tight junctions that controls passage of proteins and cells from the circulatory system. Populations of a type of immune cell called macrophages that reside at the brain borders may 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 could be affected [8]. In addition, other brain cell types such as neurons and endothelial cells have been reported to express IL-3Rα and may also respond to IL-3. Further dissecting the impact of IL-3 signaling on other cellular players will be a crucial next step.

Nonetheless, these findings are an exciting advance in understanding the role of glia 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 given the role of IL-3 and IL-3Ra in certain autoimmune disorders[9], 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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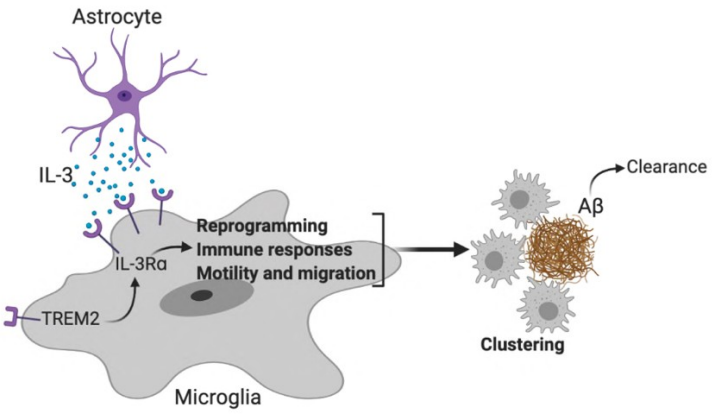
Thank you for suggesting the two figures. I'm afraid we don't really include conceptual imagery in figures for News & Views, so the first option (although engaging!) isn't really suitable. However, your second option looks good, and so I have put together a short legend for the figure below. Please check it carefully and let me know if you have any edits. In addition, please could you clarify what is meant by 'immune responses' in the figure? This seems relatively vague, so it would be good to be a bit more specific here if possible.

Figure 1 | Interleukin-3 protein signalling between cells 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 previously undiscovered signalling axis between two types of brain cells: astrocytes and microglia. 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 to cluster around Aβ plaques. Microglia have a role in clearing Aβ plaques[4], and indeed/consistent with this, McAlpine et al. found that treating AD-model mice with brain injections of IL-3 resulted in lower Aβ plaque burden in these animals. Figure adapted from Fig. X in the paper. ***[Legend OK?]***


Astrocyte
IL-3
IL-3Rα
TREM2
Reprogramming
Immune responses
Motility and migration
Microglia
Clearance
Aβ
Clustering