CHIEF SCIENTIST OFFICE

CODE: PCL/20/05

RESEARCH PROJECT BRIEFING

Analysis of Reactive Astrocytes in Alzheimer's Disease

Background and Aims

- Alzheimer's disease is a devastating condition for which we lack effective disease-modifying interventions. It is characterised by the toxic build-up of proteins called β-amyloid and tau.
- Much prior research has focused on the effects of these proteins on neurons (the nerve-cells within the brain). However, Alzheimer's disease also drives changes to another key supporting cell-type in the brain called the astrocyte. These cells play important roles for healthy brain function, providing support to nerve-cells and protecting them from injury.
- In Alzheimer's disease, astrocytes in the brain take on an appearance very different from astrocytes in the healthy brain. Whilst this was a finding first described by Alois Alzheimer himself in 1906, the nature and consequences of these astrocyte changes on brain health during Alzheimer's disease remained unknown.
- **Research question: How does Alzheimer's disease-related pathology alter astrocyte gene expression, and can astrocytes be targeted to slow disease processes associated with dementia?**

KEY FINDINGS

- Alzheimer's disease drives significant changes to the expression of astrocyte genes.
- This includes increasing the levels of astrocyte genes associated with harm as well as genes that mediate brain protection.
- Boosting the levels of protective astrocyte genes delayed the onset of functional deficits in our Alzheimer's mouse models, highlighting the potential of targeting astrocytes for therapeutic benefit.

WHAT DID THE STUDY INVOLVE AND FIND?

- We used mouse models which expressed dementia-associated mutations in genes found in families with early-onset dementia. As a result, these mice demonstrate features associated with Alzheimer's disease.

- In these mice, we used specialised methods to separate out changes in astrocytes from those in the other brain cell-types. This involved using mice with mutations causing astrocytes specifically to be labelled with a florescent protein, allowing us to separate out changes in astrocytes from those of other surrounding cells. This allowed us to understand the molecular pathways altered in astrocytes in response to Alzheimer's disease.

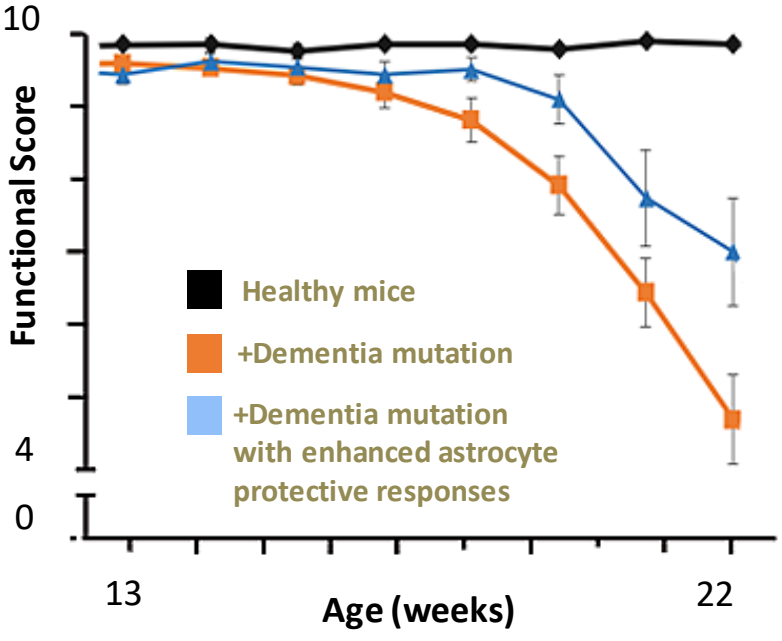
- We found that astrocytes have a complex response during Alzheimer's disease. They increased expression of genes in both potentially neurotoxic as well as protective pathways. We discovered that the latter protective response was controlled by a master regulator protein called Nrf2. Hypothesising that this signature may represent an astrocyte protective response that was "too little, too late", we set out to understand what would happen this was boosted in early disease.

- We increased the levels of the Nrf2 protective regulator in astrocytes in our mouse models of Alzheimer's disease, and found that this led to reduced neuronal loss and delayed the onset of physical deficits (See Figure).

- Hence, these studies reveal the protective potential of astrocytes to reduce Alzheimer's disease associated brain damage.

Functional loss in transgenic mice exhibiting dementia-causing mutations mirrors the age-related decline seen in patients.

Upregulating protective astrocyte responses slows this decline.



WHAT IMPACT COULD THE FINDINGS HAVE?

- This laboratory-based work highlights a potential role for astrocytes as a previously under-studied cell-type that could be targeted for therapeutic benefit in patients with early Alzheimer's disease.

- Future clinical studies are now needed to understand whether the above findings hold true in patients with Alzheimer's disease and if this can be translated to clinical practice.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- The work was published in a peer-reviewed open-access journal, where it can be read for free by anyone: **Reference: Jiwaji Z. *et al*. Reactive astrocytes acquire neuroprotective as well as deleterious signatures in response to Tau and Aß pathology. Nature Commun. 13, 135 (2022).** The work has also been presented at several national and international scientific meetings to other researchers investigating treatments for dementia.

- The data from the gene-expression studies was uploaded to an open-access public repository (European Nucleotide Archive) to enable access to other scientists in the field.

CONCLUSION

- Alzheimer's disease alters astrocytes in the brain in complex ways, including driving both deleterious as well as neuroprotective effects.

- The latter, if enhanced, slows disease progression in our mouse models of Alzheimer's disease.

- Overall, these findings highlight a potential role for modulating astrocytes for therapeutic benefit to slow disease progression in Alzheimer's disease.

RESEARCH TEAM & CONTACT

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