How does the protein tau cause neurodegeneration in Alzheimer's Dementia?

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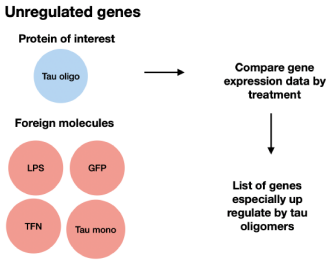
Introduction

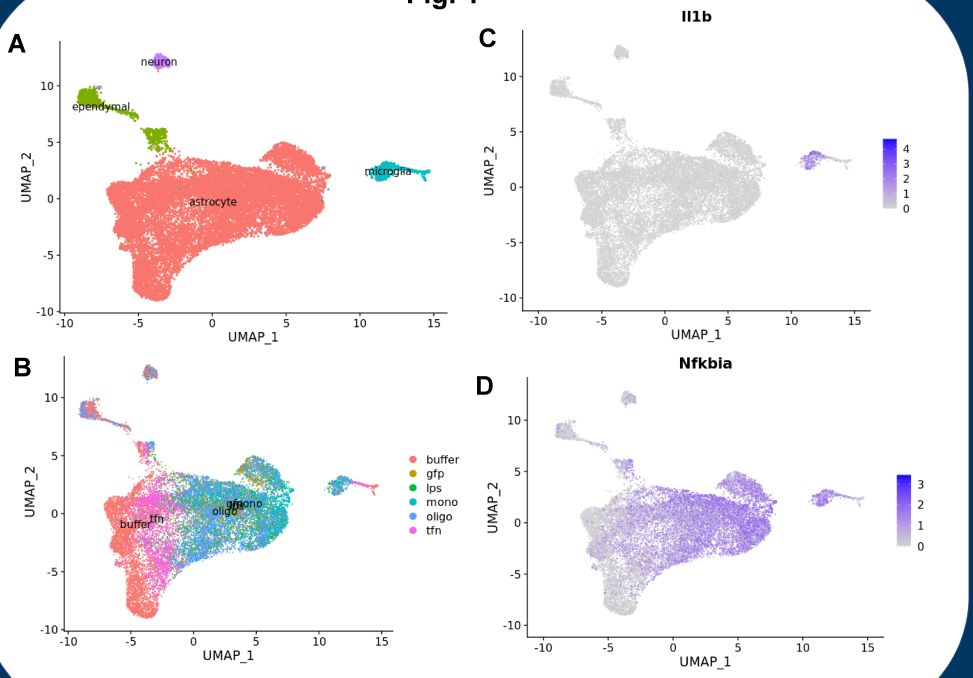
Tau oligomers, which are small aggregates of the protein tau, have been found to drive neuron death in Alzheimer's Dementia (AD)[1]. The goal of this project is to identify possible pathways and intermediates involved in tau oligomer mediated neuron death. By analyzing RNA sequencing data, we found that the Nlrp3 inflammasome may play a pro-apoptotic role in this mechanism.

Methods



- Received single cell RNA sequencing data from mouse brain tissue cultures infected with either tau oligomers or one of four other molecules.
- Analyzed data with Seurat in RStudio and found a list of genes especially altered by tau oligomers.
- Analyzed gene list with Metascape and GOrilla and found signaling pathways of interest.

Fig. 1



Results

We found in our Metascape and GOrilla analysis that genes especially upregulated by tau oligomers had functions related to the NFkB pathway. In fact, Metascape, using TRRUST, predicted that the Nfkb1 gene is very likely a transcriptional regulator in astrocytes and neurons infected with tau oligomers.

(Fig. 1) Cells mapped by their genetic similarity.

- (A) Cells labeled by their cell type.
- (B) Cells labeled by the molecule their culture was infected with.
- (C) Interleukin-1 beta (Il1b), which activates the NFkB pathway, is highly expressed in microglia infected with tau oligomers.
- (D) Nfkbia (NFkB inhibitor alpha), is especially upregulated in cells infected with tau oligomers. Astrocytes and neurons in tissue cultures infected with tau oligomers show an average Nfkbia expression of 7.86E+34 and 3.05E+05 respectively. Both values are the highest out of all treated groups.

Discussion

The NFkB pathway is activated in tissue cultures infected with tau oligomers, as indicated by an upregulation of the Il1b activation factor. The upregulation of Nfkbia in astrocytes and neurons is evidence that Il1b, a secreted protein[2], is taken up by and activates the NFkB pathway in astrocytes and neurons. The fact that Nfkbia expression is especially upregulated by tau oligomers, and that Nfkb1 is a predicted regulator for this set of cells, suggests that the NFkB pathway plays a role in tau oligomer mediated neuron death. Specifically, we hypothesize that the NFkB pathway activates the Nlrp3 inflammasome, which has already been implicated in neuron death[3]. Future directions for this project include testing whether the NFkB pathway is really a pro-apoptotic factor using in vitro experiments.

Literature Cited

1. Guerrero-Muñoz, M. J., Gerson, J., & Castillo-Carranza, D. L. (2015). Tau Oligomers: The Toxic Player at Synapses in Alzheimer's Disease. Frontiers in cellular neuroscience, 9, 464.
2. Brough D, Rothwell NJ. Caspase-1-dependent processing of pro-interleukin-1beta is cytosolic and precedes cell death. J Cell Sci. 2007 Mar 1;120(Pt 5):772-81.
3. Ising, C., Venegas, C., Zhang, S. et al. NLRP3 inflammasome activation drives tau pathology. Nature 575, 669–673 (2019).

Acknowledgments

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For further information

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