Trisomy 21–induced dysregulation of microglial homeostasis in Alzheimer's brains is mediated by USP25

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Speaker info

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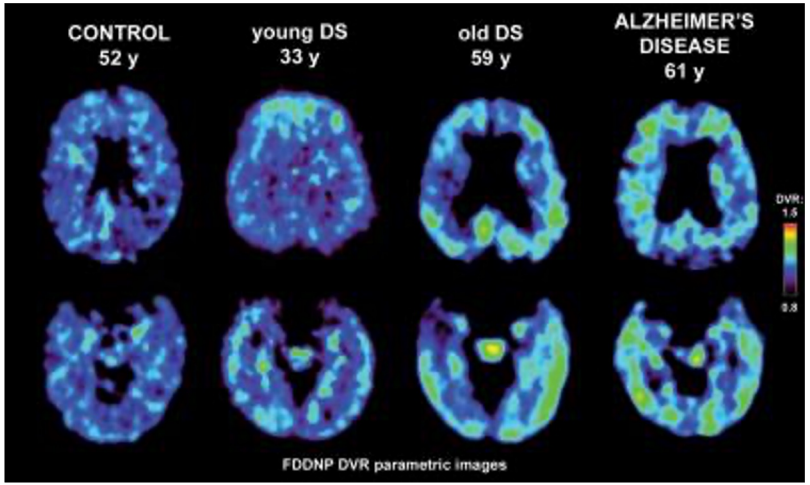
Alzheimer disease and Down syndrome

Down syndrome (Trisomy 21; DS) is the most common cause of intellectual disability

DS is also the most common risk factor for early onset Alzheimer disease (AD)

Although some causes are hypothesized (eg, APP on chromosome 21), the genetics underlying this association are unknown



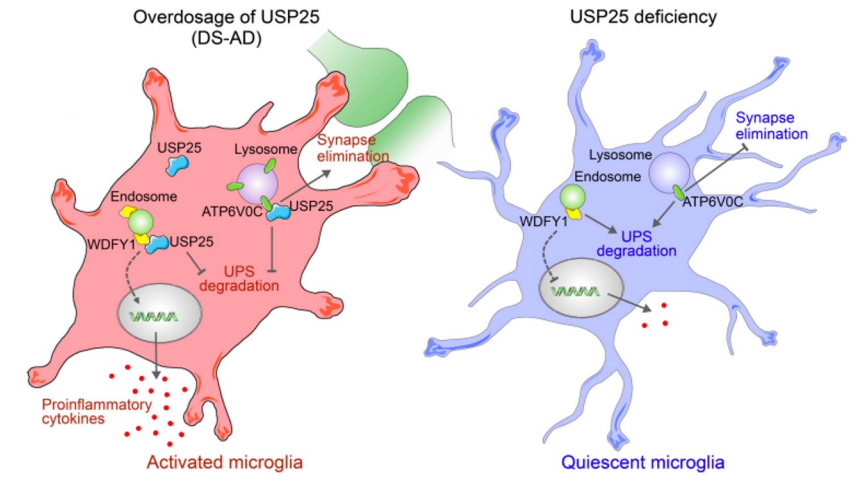
FDDNP PET illustrating tau distribution in DS and AD[1]

Microglia and USP25

Microglia are the major immune cells of the brain and coordinate immune response

The ubiquitin-proteasome system (UPS) is an essential protein breakdown mechanism. UPS defects cause neurotoxic accumulation

USP25 is a gene essential to this pathway located on chromosome 21



What this paper accomplishes

This paper elaborates on the role of *USP25* in neuroinflammation, in the context of upregulation due to trisomy 21. Specifically:

1. Trisomy of chromosome 21 genes promotes neuroinflammation
2. Deletion of *USP25* reverses cognitive and synaptic deficits in mouse AD model
3. Deficiency of USP25 increases proteasomal degradation
4. Inhibition of USP25 decreases neurological dysfunction in mouse AD model

Methods

Mouse models

There are six mouse models in the paper

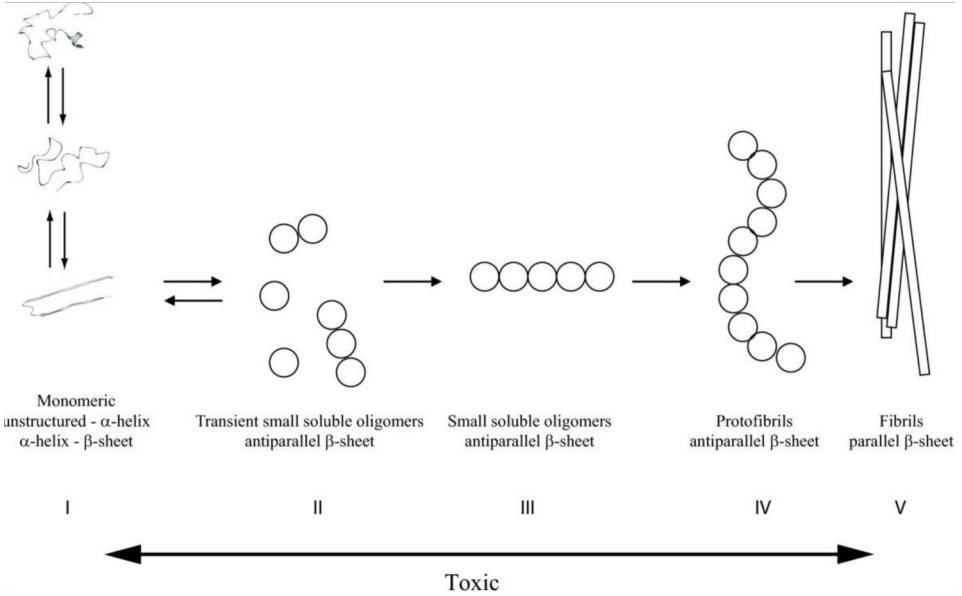
- Wild type: control mouse model
- Dp16: DS model
- 5xFAD: AD model
- Dp16;5xFAD: cross of DS and AD models
- BAC-Tg-USP25;5xFAD: upregulation of USP25 in AD model
- *Usp25*+/- 5xFAD: deletion of *USP25* in AD model

Amyloid-β oligomer injection and clearance

To test function of USP25 (and related proteins), Aβ oligomers were injected into the mouse hippocampus

Small interfering RNAs (siRNAs) were used to silence *Atp6v0c* (ATP6V0C is not degraded when *USP25* is deleted)

This was followed by immunohistochemical analysis of Aβ induced microglial phagocytosis



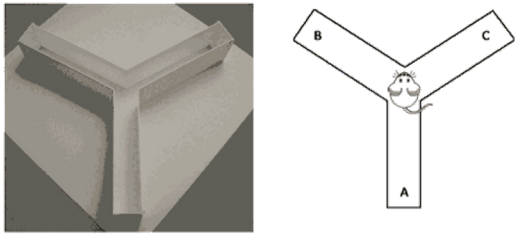
Assembly of amyloid-β oligomers[2]

Electrophysiology and tasks

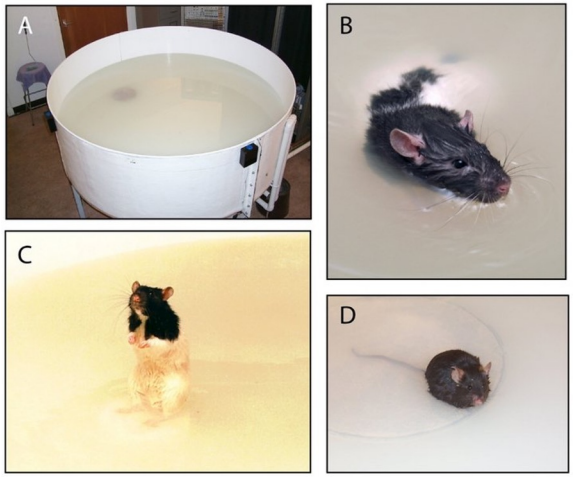
Field Excitatory Postsynaptic Potentials (fEPSPs) were measured in cell samples

Three behavioral paradigms were used to assess neurological impairment:

- Y-maze
- Morris water maze (MWM)
- Fear conditioning (FC)



Y-maze[3]



MWM[4]

AZ1 administration

AZ1, an inhibitor of USP25, was used to demonstrate the reversal of neuroinflammatory effects

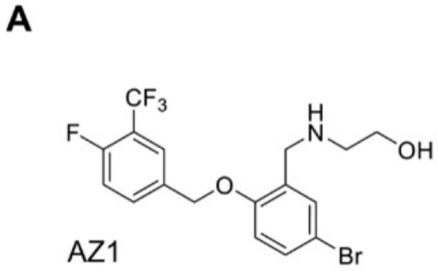


Figure 6a

Chronic AZ1 injections were performed (see figure) and the same behavioral biochemical assessments were done

Figure 6c

Results

Characterization of genes associated with DS and AD

To characterize the genes upregulated in DS and AD, the 5xFAD;Dp16 mice were used

Gene ontology was used to identify the pathways most implicated in the cross-breed compared to 5xFAD

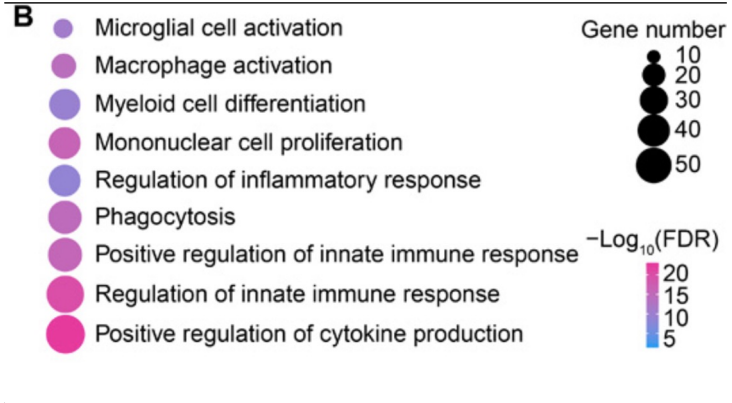
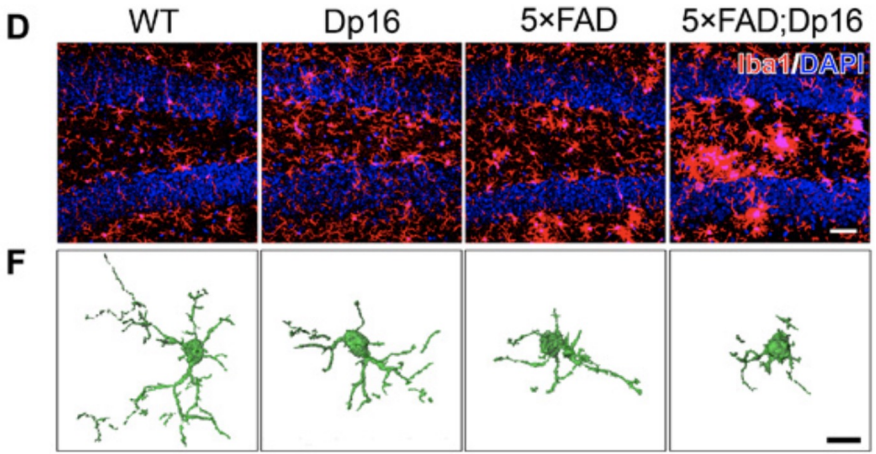


Figure 1b

Microglial proliferation in DS and AD

Increased proliferation of microglia is observed in both AD and DS, with an even greater increase in ADxDS model

This is accompanied by an increase in microglial soma size and a decrease in total processes



- Wild type: control mouse model
- Dp16: DS (down syndrome) model
- 5xFAD: AD (alzheimers) model
- Dp16;5xFAD: cross of DS and AD models
- BAC-Tg-USP25;5xFAD: upregulation of USP25 in AD model
- *Usp25*-/- 5xFAD: deletion of *USP25* in AD model

Microglial proliferation

Explicit quantification was performed of microglial cell number in the hippocampus

Soma cell size and total processes were also quantified

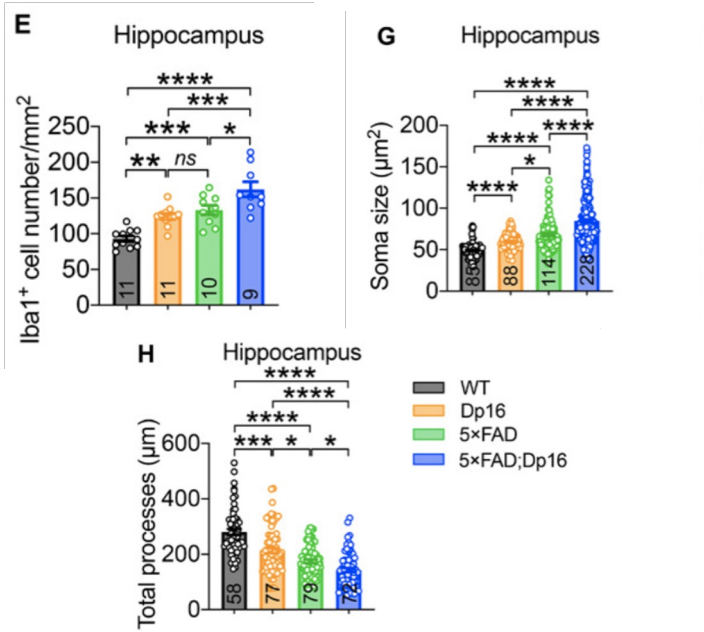


Figure 1e, g, h

Overexpression of *USP25* produces similar results

Adding a copy of *USP25* to the wild type and 5xFAD mice produces an increase in microglial proliferation

This is accompanied by similar morphological changes seen in the ADxDS mouse model

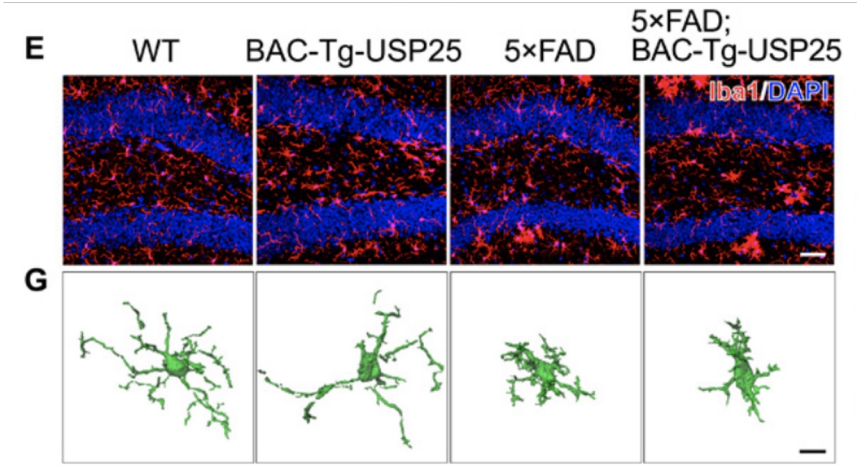


Figure 2e, g

Microglial proliferation

As in the ADxDS model, explicit quantification was performed of microglial cell number in the hippocampus

Soma cell size and total processes were also quantified

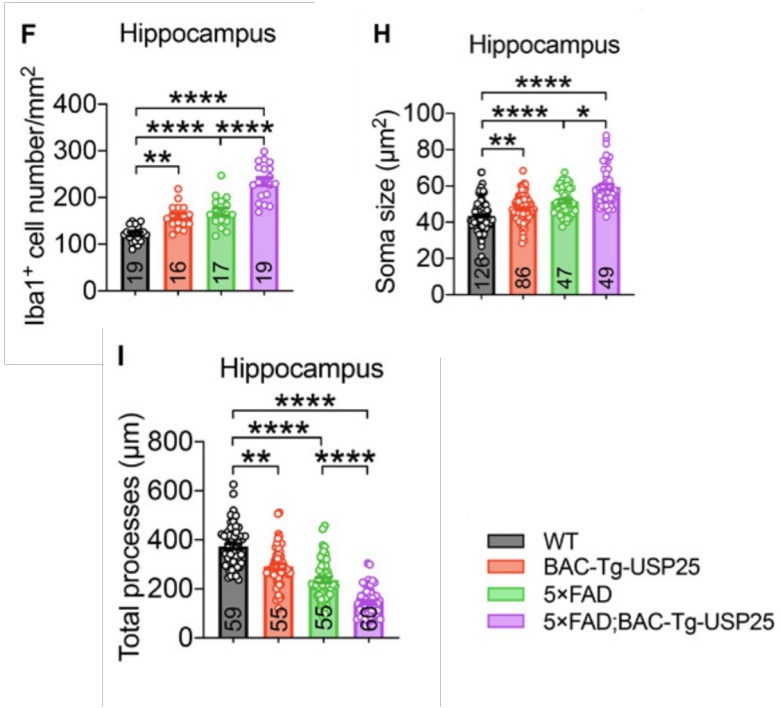


Figure 2f, h, i

Hippocampal neuron impairment

In the BAC-Tg-USP25;5xFAD model, the increase in microglial activity corresponds to hippocampal neuronal impairment

Specifically, the number of dendritic spines is decreased in the hippocampal neurons

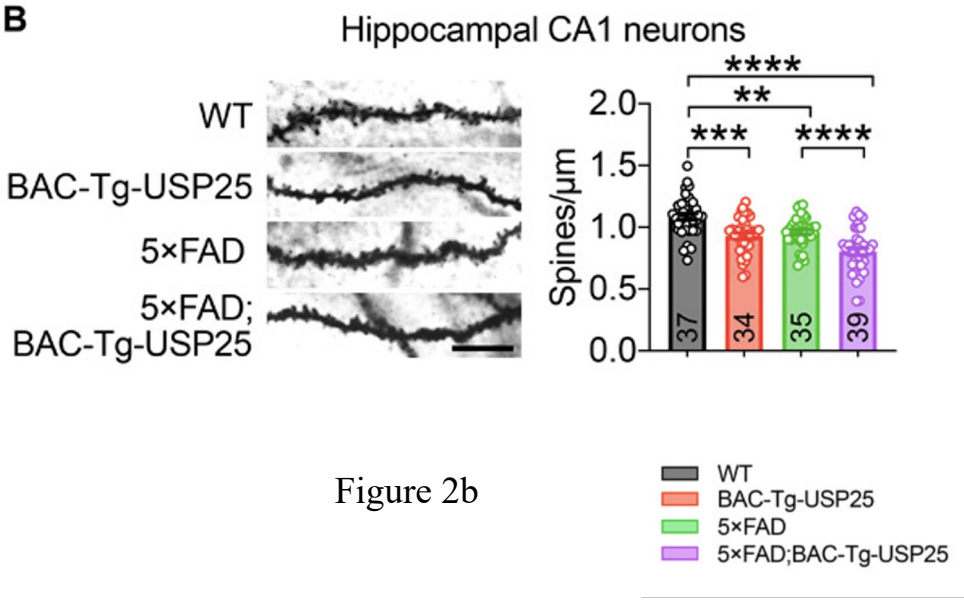


Figure 2b

Loss of synapses are associated with functional deficits

This loss of dendritic spines is associated with a functional deficit as well

fEPSP amplitude is significantly reduced in the presence of BAC-Tg-USP25

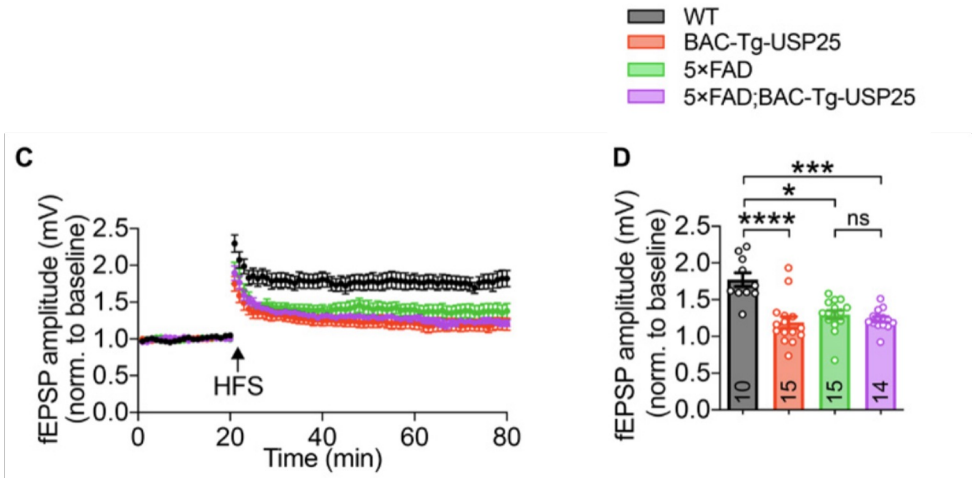


Figure 2c, d

Neuronal deficits are associated with behavioral decline

In the presence of BAC-Tg-USP25, there is a significant behavioral decline observed (above and beyond decline present in 5xFAD)

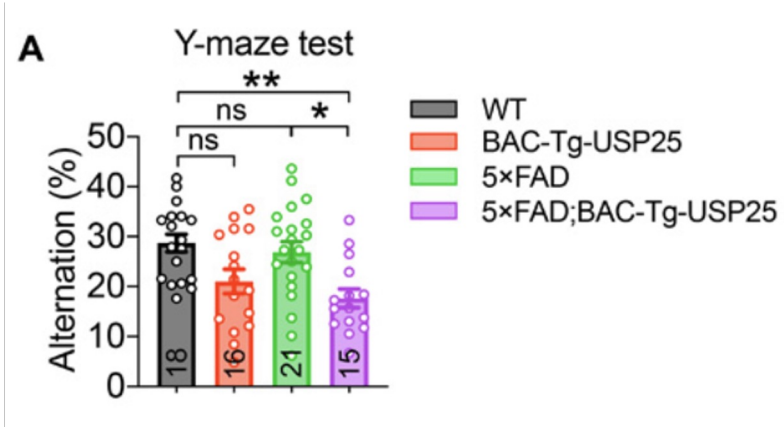


Figure 2a

Deletion of *USP25* enhances synaptic and cognitive function

The next section asks: can deletion of *USP25* reverse some of the effects observed in 5xFAD?

5xFAD;*Usp25*+/- mice showed an increased number of dendritic spines, on par with control

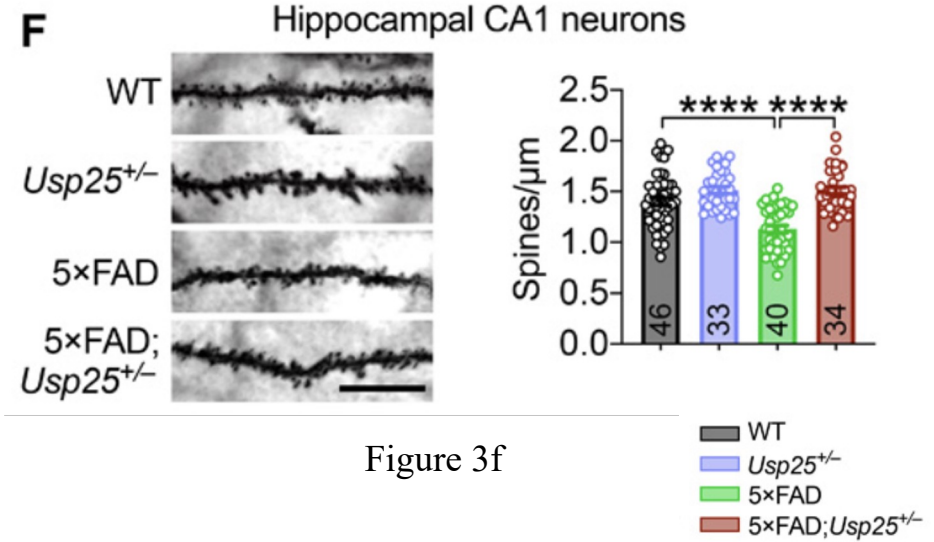


Figure 3f

Deletion of *USP25* improves electrophysiological response

5xFAD;*Usp25*+/- mice also showed an recovered fEPSP amplitude compared to 5xFAD mice

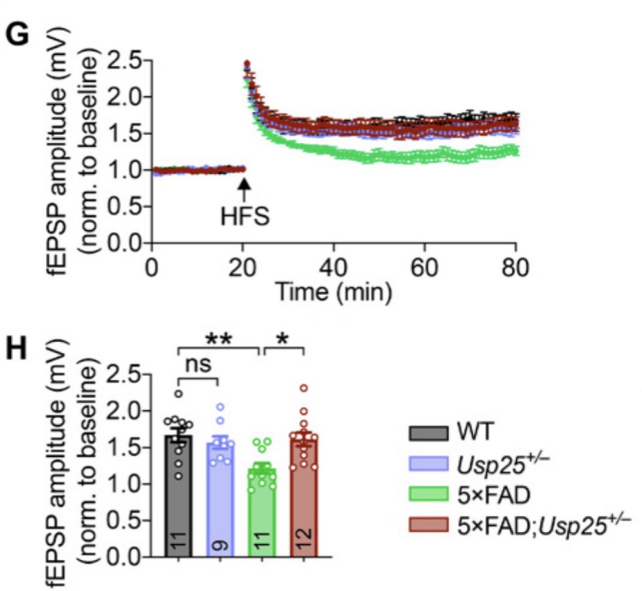


Figure 3g, h

Deletion of *USP25* improves behavioral function as well

5xFAD;*Usp25*+/- mice showed improved alternation in the Y-maze task relative to 5xFAD mice

They also showed recovered learning in FC contextual task, and improved learning in the FC cued test (although not as high as control)

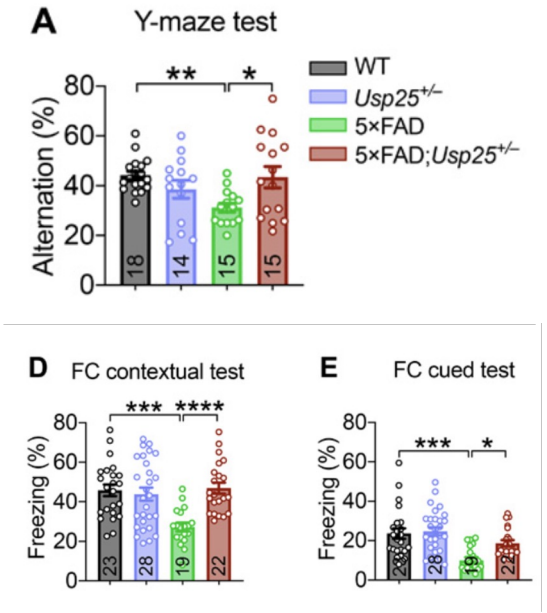


Figure 3a, d, e

Deletion of *USP25* improves behavioral function as well

Finally, 5xFAD;*Usp25*+/- mice showed improved learning in the MWM training and probe tests, indicating improved memory over 5xFAD

Taken together, this evidence suggests that *USP25* deletion helps ameliorate the pro-inflammatory state in 5xFAD

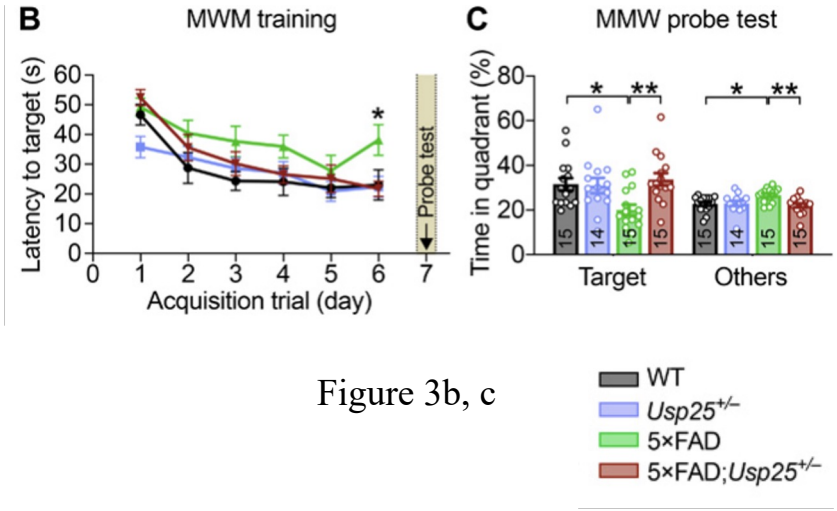


Figure 3b, c

Deletion of *USP25* reduces microglial proliferation

To confirm this, the effect of *USP25* deletion on microglial proliferation was also assessed

5xFAD;*Usp25*+/- mice showed decreased microglial proliferation relative to 5xFAD mice, as well as decreased synaptic engulfment (PSD95 probe)

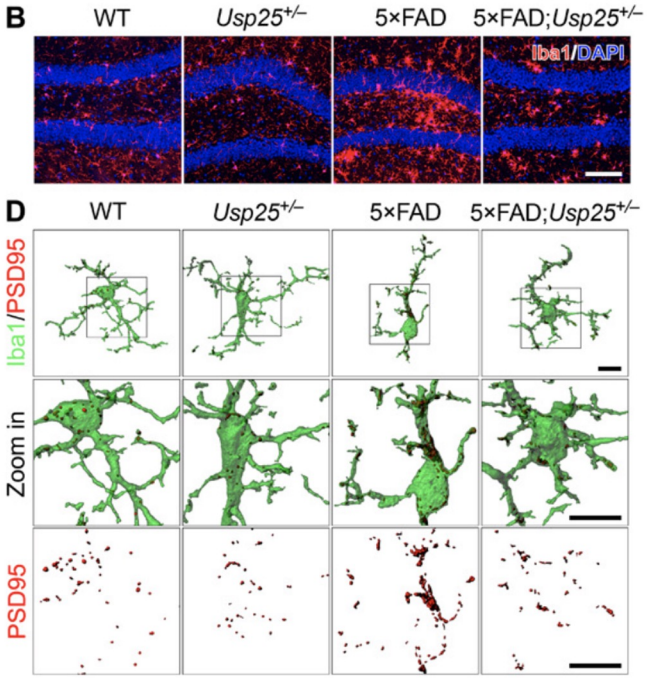


Figure 4b, d

Deletion of *USP25* reduces microglial proliferation

To directly quantify these changes, 5xFAD;*Usp25*+/- mice showed decreased microglial number in the hippocampus, decreased soma size, and increased number of processes

Interestingly, the number of processes did not recover to baseline as the other two metrics did

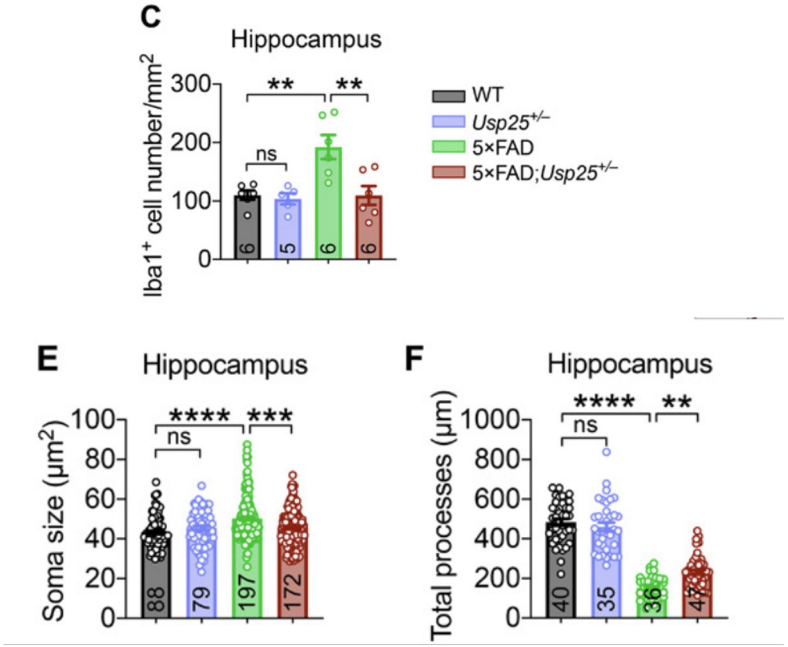


Figure 4c, e, f

Deletion of *USP25* downregulates inflammatory signalling

5xFAD;*Usp25-/-* mice showed a decrease in several pro-inflammatory signalling pathways (notably the TLR4 pathway), indicating that USP25 regulation of inflammation is multifactorial

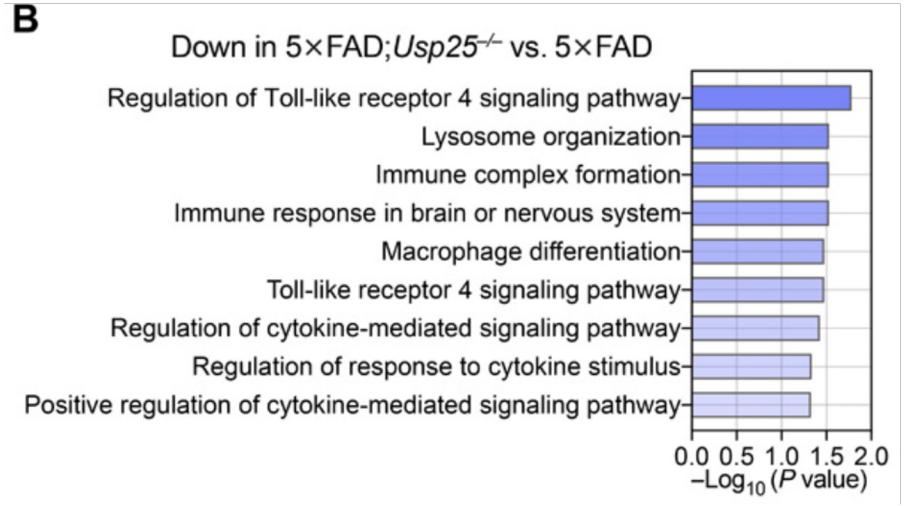


Figure 5b

Deletion of *USP25* reverses $A\beta_{42}$ driven synapse engulfment

The presence of USP25 stabilizes Atp60vc, which causes increased synaptic degradation by microglia in the presence of $A\beta_{42}$

By inhibiting Atp6v0c directly, there is an observable decrease in synaptic engulfment, which further implicates the downstream effects of USP25 in neurodegeneration

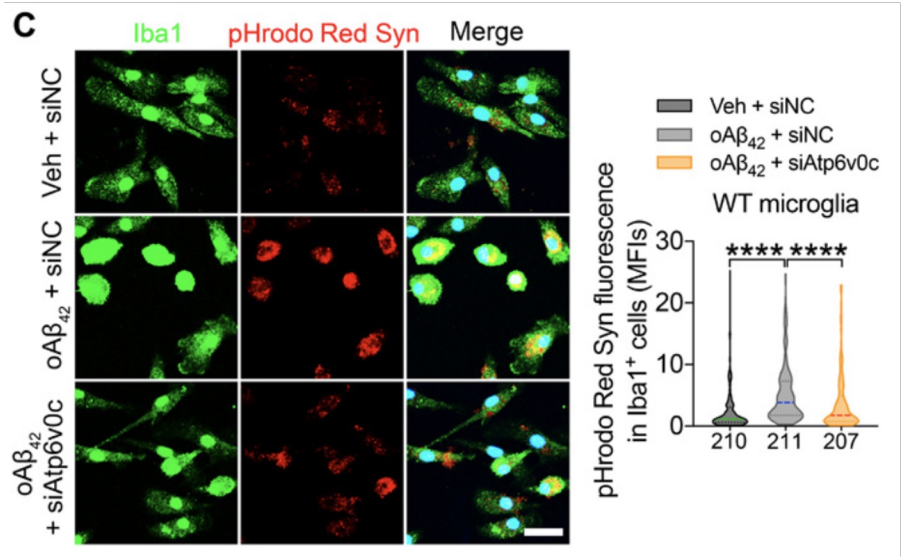


Figure 5c

Inhibition of USP25 via AZ1 partially reverses microglial proliferation

To explore a potential treatment targeting USP25, the drug AZ1 was administered to 5xFAD mice to observe the effects of reducing USP25 activity in AD

There was a noticeable decrease of microglial proliferation (shown here), as well as an improvement of fEPSP activity and behavioral metrics

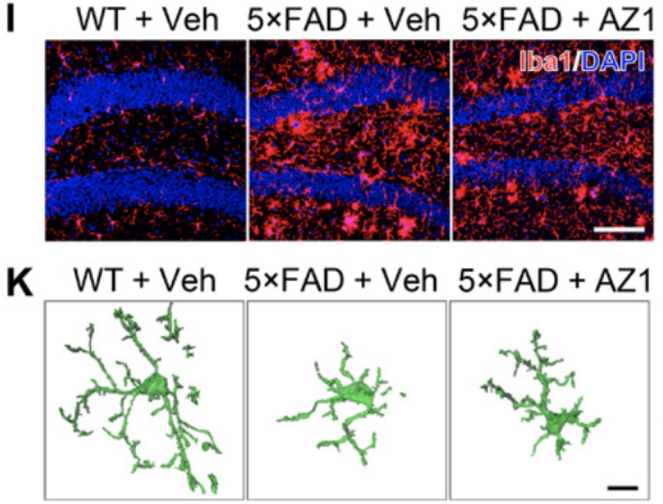


Figure 6i, k

Discussion

What this paper accomplishes

This paper elaborates on the role of *USP25* in neuroinflammation, in the context of upregulation due to trisomy 21. Specifically:

1. Trisomy of chromosome 21 genes promotes neuroinflammation
2. Deletion of *USP25* reverses cognitive and synaptic deficits in mouse AD model
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Strengths of this paper

This paper presents a *very* detailed analysis of the USP25 system in a mouse AD model including:

- Implications in DS as well as AD
- Showing both increased USP25 is damaging and decreased USP25 is protective
- Exploring a downstream pathway involving proteins stabilized by USP25 presence
- Potential treatment opportunity targeting USP25 for inhibition

Limitations and future directions

No study is without limitations, and of course there are a few for this study

- The role of Aβ in AD is not fully understood, and has been questioned in more recent literature
- This work is obviously in mouse models, so translation to humans is not necessarily guaranteed

Future work ideas:

- Studying USP25 as a potential treatment target in humans would be an interesting path forward, especially if AZ1 can be used safely

Citations

Paper presented here:

Zheng Q, Li G, Wang S, Zhou Y, Liu K, Gao Y, Zhou Y, Zheng L, Zhu L, Deng Q, Wu M, Di A, Zhang L, Zhao Y, Zhang H, Sun H, Dong C, Xu H, Wang X. Trisomy 21-induced dysregulation of microglial homeostasis in Alzheimer's brains is mediated by USP25. Sci Adv. 2021 Jan 1;7(1):eabe1340. doi: 10.1126/sciadv.abe1340.

Image credits (if not directly cited, images come from the paper under discussion)

[1] UCLA FDDNP PET https://www.eurekalert.org/news-releases/656164

[2] Broersen K, Rousseau F, Schymkowitz J. The culprit behind amyloid beta peptide related neurotoxicity in Alzheimer's disease: oligomer size or conformation? Alzheimers Res Ther. 2010 Jul 14;2(4):12. doi: 10.1186/alzrt36.

[3] Y-maze illustration:
https://med.stanford.edu/sbfnl/services/bm/lm/_jcr_content/main/panel_builder/panel_1/text_image_5.img.full.high.png/ymaze.gif

[4] Morris Water Maze illustration: : http://www.scholarpedia.org/article/Morris_water_maze