nature portfolio

Peer Review File

Priming of CD8+ T cells by peripheral dendritic cells exacerbates tau-mediated neurodegeneration in brain

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This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Neuroscience.

Version 0:

Reviewer comments:

Reviewer #2

(Comments for the Author)
In this revised version, the authors have largely answered earlier queries. The paper would now seem acceptable in principle for publication in Nature Neuroscience.

The point by point reply to the last set of referees' comments is discussed below (numbering as per earlier comments and authors' latest rebuttal)

1. The authors argue that there are no additional models besides WDFY4 KO mice to assess cross-presentation by cDC1. This is not entirely true (e.g., RAB43 KO mouse published by co-author K. Murphy). They also argue that generating a conditional KO mouse selectively lacking WDFY4 in cDC1 is unreasonable. There are simpler ways to do it. For example, the authors could have considered making a mixed chimera with WDFY4 KO and Irf8delta32 bone marrow. Anyway, the suggestion at this stage is not to carry out additional experiments but to capture the limitations of the model by appropriate wording and acknowledge explicitly that the data are suggestive rather than conclusive that "cDC1 mediated cross-presentation is critical for CD8+ T cell responses in the brain".
2. OK
3. It would still seem important to show numbers of cDC2s as their percentage is influenced by the absence of cDC1s.
4. OK. Maybe the authors can highlight that the endogenous source of antigens that are being cross presented is not known.
5. OK, although one should be careful with the interpretation of deleting cells that are (almost) not present to start with.
6. OK
7. OK
8. OK.
9. OK
10. OK

(Remarks on code availability)

Response to reviewers

We thank the reviewers for their comments on the revision to our manuscript. Below we respond to their comments. Any changes to the manuscript are in RED.

Referee #2 (Remarks to the Author):

In this revised version, the authors have largely answered earlier queries. The paper would now seem acceptable in principle for publication in Nature Neuroscience.

The point-by-point reply to the last set of referees' comments is discussed below (numbering as per earlier comments and authors' latest rebuttal)

Authors' response: We thank the reviewer for their comments. In this letter, we only focused on the remaining questions raised by the reviewers.

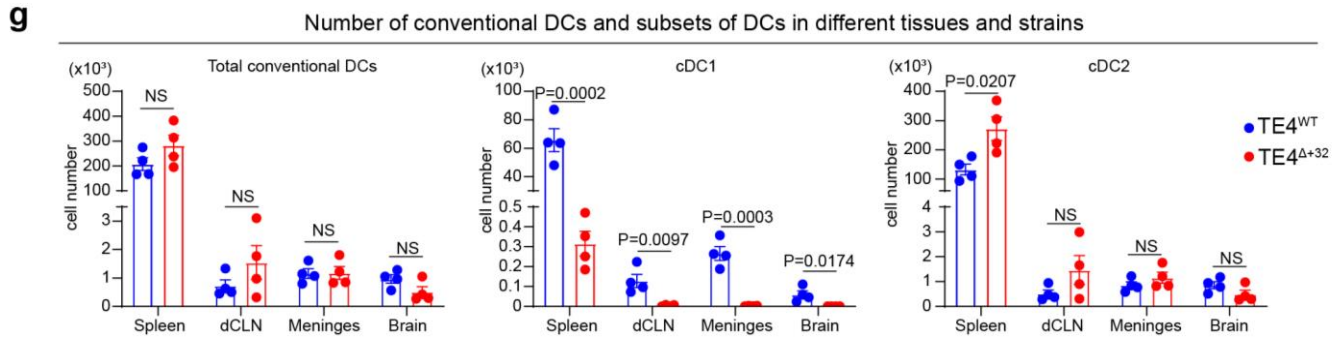
1. The authors argue that there are no additional models besides WDFY4 KO mice to assess cross-presentation by cDC1. This is not entirely true (e.g., RAB43 KO mouse published by co-author K. Murphy). They also argue that generating a conditional KO mouse selectively lacking WDFY4 in cDC1 is unreasonable. There are simpler ways to do it. For example, the authors could have considered making a mixed chimera with WDFY4 KO and Irf8delta32 bone marrow. Anyway, the suggestion at this stage is not to carry out additional experiments but to capture the limitations of the model by appropriate wording and acknowledge explicitly that the data are suggestive rather than conclusive that "cDC1 mediated cross-presentation is critical for CD8+ T cell responses in the brain".

Authors' response: We agree with the reviewers and re-word in the main text to acknowledge that the data suggest that cDC1 mediated cross-presentation is critical for CD8+ T cell responses in the brain in lines 347-350.

3. It would still seem important to show numbers of cDC2s as their percentage is influenced by the absence of cDC1s.

Authors' Response: We performed the experiment quantifying the actual number of total conventional DCs, cDC1, and cDC2 cells in spleen, dCLN, meninges, and brains. We have added the data to the Extended data Fig. 1g. For the convenience of the editors to evaluate the data, we have inserted a copy of the plotted data below (Figure R1). As shown, in all four tissues, there were no obvious changes in total conventional cDCs. The numbers of cDC1 cells cannot be detected in all four tissues of $TE4^{\Delta+32}$ mice. Numbers of cDC2 cells showed a significant increase in spleen due to the absence of cDC1s in $TE4^{\Delta+32}$ mice. In dCLN and meninges, there was a trending but not significant increase of cDC2s due to the relatively low abundance of the cDC1 in these tissues. In brain (hippocampus and cortex), both total conventional cells and cDC2 cells were not significantly changed and even showed a treading decrease in $TE4^{\Delta+32}$ mice, which was largely due to the lower inflammatory responses in the brain.

Figure R1



4. OK. Maybe the authors can highlight that the endogenous source of antigens that are being cross presented is not known. (Original question: 4. OVA-loaded cells: The relevance of intracranial injection of osmotically loaded OVA cells to physiological antigen cross-presentation during tauopathy remains unclear. The authors assume a direct role for cDC1s, yet alternative mechanisms—such as antigen transfer from migratory APCs to LN-resident cDC1s—are not excluded.)

Authors' Response: We agree with the reviewers' comments and have made the changes accordingly.

5. OK, although one should be careful with the interpretation of deleting cells that are (almost) not present to start with. (original question: 5. Localization of cDC1s: The manuscript notes a near absence of cDC1s in the brain, raising questions about where cross-presentation occurs. The disease state in TE4 mice may influence antigen leakage, APC activation, and migration, all of which could affect cross-presentation dynamics.)

Author's Response: We made careful interpretation that the antigen presentation occurred predominantly in the periphery and cDC1 infiltration was low even with severe neurodegeneration.