Review of: "Synapse Weakening-Induced Caspase-3 Activity Confers Specificity to Microglia-Mediated Synapse Elimination"

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Potential competing interests: No potential competing interests to declare.

In this manuscript, the authors studied the mechanisms of activity-dependent synapse elimination during development. As a model system, they used the well-known mouse retinogeniculate visual system and examined the role of caspase-3 as a molecular candidate involved in the process of synapse elimination.

The data presented show convincingly that, in the visual system, caspase-3 activation is essential for activity-dependent synapse elimination of weak synapses. They also identified microglia as the effectors of caspase-3-activated synaptic elimination. Finally, the involvement of caspase-3 activation in the developmental synapse elimination is extended to the synapse loss observed in adult neurodegenerative disease. Indeed, in a mouse model of Alzheimer's disease, caspase-3 deficiency protects against amyloid-β-induced synapse loss.

Overall, the data are well presented. The system and the techniques used are well described and well validated (cf. Figures S1, S2, S3, S5, S7). The results are convincing and clearly bring new information about the key role played by caspase-3 in the process of developmental synapse elimination as well as in the synapse loss observed in neurodegeneration.

Some minor points can be improved.

Figure 1B: Caspase-3 activation is shown as nuclear or somatic labeling. An inset in the figure at higher magnification with DAPI staining would allow for a precise location of the caspase-3 labeling. This labeling raises the question of the presence of apoptotic cells. This point should be examined. Again, a double labeling with DAPI staining could help to exclude or not this hypothesis.

Figure 1E: Caspase-3-activated positive cells appear easily identifiable by their somatic labeling. So, instead of using the method described in the manuscript, why not quantify caspase-3 activation by simply counting the caspase-3 positive cells? This should be done or discussed if it is not possible.

Figure 1F: A DAPI staining would allow for the visualization of the localization of cells.

Figure 2: Results are convincing and well presented. As proposed for Fig. 1, the quantification of the activated caspase-3 signal could be done by counting caspase-3 positive cells.

Figure S9A:

- The legend of Figure S9 should be changed. The term “activation” for microglia includes changes in morphology, phagocytosis, but also expression of inflammatory markers, etc..

- The microglial density shown by IBA1 labeling appears to be lower in Casp3 -/- dLGNs. A quantification of IBA1+ microglia in the dLGN of casp3+/+ and casp3-/- mice should be performed.

- An image showing the CD68 labeling in IBA1+ microglia would allow for the validation of the quantification shown in Fig. S9 C-D.

- The legend of S9 C-D should be changed to “quantification of microglia phagocytic capacity.” Indeed, as CD68 is a lysosomal marker, the CD68 labeling gives only an evaluation of the phagocytic capacity

Fig. 7:

- The mouse model of App/Ps1 should be better described. The genotypes of the App/Ps1 mice used should be explained. The use of App/Ps1-/- as a control is confusing. The term -/- is generally used for mutant mice. It is also not clear why the synapse loss is examined in App/Ps1$^{+/-}$ heterozygous mice and not in homozygous mice.

General remark:

Except in the last part concerning the mouse model App/Ps1, the sex of the animals used is not known. This should be specified and may be discussed. Indeed, it is known that there are sex differences in microglia concerning their morphology, number, function...(cf. Bordt, E et al. Glia 2020). Furthermore, as it is shown in Fig. S13, the App/PS1 model exhibits clear differences in the amyloid deposit between males and females. The role of caspase-3 in the synapse loss of App/PS1 male mice should be discussed.