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 paper, the authors investigate whether casp 3 activation is the targeting signal that leads to synaptic elimination in the visual system during development by examining the retinal projections to the dorsal lateral geniculate nucleus in the early developmental spontaneous refinement of synapses and in the later activity-based development upon light stimulation. In both stages of synapse elimination, casp3 activation is involved in tagging the postsynaptic compartment and leading to the elimination of weak synapses. The authors show that the process is based on competition between functionally strong and weak synapses. In casp3 -/- mice, the elimination is disrupted. In the casp3-/+ mice, the deficits in post-synaptic targeting by casp3 reduce microglia elimination of synapses but leave less affected astrocyte-mediated elimination. They then show that casp3 is also involved in Ab-mediated synapse elimination in the App/PS1+/- mouse model of AD. They analyze the dentate gyrus and show preservation of synaptic density in the casp3-/-/App/PS1+/- mice without an associated reduction in plaque or microgliosis, suggesting that the protection occurs independent of changes in Ab accumulation and microgliosis.

Strengths

The data supporting the conclusions are backed up by strong, state-of-the-art, and well-designed quantitative approaches. The data demonstrate a role of postsynaptic casp 3 activation in the developmental synaptic elimination in the visual system and a likely role in synapse loss in a neurodegenerative model of AD. The data hold mechanistic and translational significance, especially for the AD model.

Weaknesses

The difference in signaling function of casp 3 in microglia and astrocyte-mediated synapse elimination is interesting; however, astrocytic synaptic removal is still present and statistically significant in casp3-/- (Fig S11, C). This result may indicate a hierarchy of signaling for astrocytic phagocytosis vs. microglia or a threshold effect of casp 3 activation at the post-synaptic space. It would be helpful to use the casp3+/+ rather than casp3+/- to fully measure the effect mediated by astrocytes. The synapse elimination will be full in the casp3+/+ mice vs. casp3+/- and will lead to a greater difference with the casp3/-.

While the data in the AD model are very interesting, the analysis is less well developed than that of the developmental

model. The absence of casp3 activation in the 6-month-old females, where there is a reduction in the synaptic loss, may indicate that the engulfment occurs earlier and/or, as the authors suggest, is stochastic. It would be helpful to measure synapse loss in the DG of the mice showing high casp3 activation vs. low casp 3 activation at 4 months. The high casp 3 is expected to result in higher synapse loss. This would establish a more direct link between casp3 activation and synapse elimination by microglia.

The sequence of figures is, at times, difficult to follow and requires switching between figures to follow the data presentation. The authors could consolidate the data in a more streamlined manner. For example, label the supplementary as extended data for each main figure? For example, S14, S15, S16 could be consolidated in one figure as extended data for Fig. 7.