PEER-REVIEW REPORT 1

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Title: Loss of canonical Wnt signaling is involved in the pathogenesis of Alzheimer's disease
Reviewer's Name: Yun-Bae Kim
Reviewer's country: Korea
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COMMENTS TO AUTHORS

In the review, the authors explained the role of dysfunction of Wnt signaling in the amyloidogenesis, as a possible triggering factor of Alzheimer disease (AD). The review may provide readers with a good information on the pathobiology of AD.

1) Although Purro et al. (2012) demonstrated that an increased level of the Wnt/β-catenin antagonist Dkk-1 is necessary to produce Aβ-mediated synaptic loss, there is no evidence of relationship with Aβ peptide accumulation and neurotoxicity (independent of Aβ peptide?). It is necessary to clarify whether synaptic failure alone related to impaired Wnt/β-catenin (without Aβ-mediated synaptic loss) can result in memory deficits.

2) Although activation of Wnt/β-catenin signaling recovers the hippocampus-dependent cognitive impairment, no detailed mechanism(s) were suggested how acetylcholine, a cholinergic neurotransmitter responsible for memory acquisition, can be restored. It there any reports that Wnt/β-catenin signaling in the cholinergic nervous system plays a role for acetylcholine synthesis via activation of choline acetyltransferase?

3) For elimination of accumulated Aβ, enzymes neprilysin and insulysin from microglia are required. It is recommended that any relationship between Wnt/β-catenin signaling and Aβ elimination (via microglial activation?) should be described.