

OPEN PEER REVIEW REPORT 1

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Title: TLR2 and TLR4-mediated inflammation in Alzheimer's disease: self-defense or sabotage?

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COMMENTS TO AUTHORS

In this manuscript the authors bring a new highly relevant research topic. The text is very well described and very direct. And the treatment proposal they bring to AD is clear.

In general, the manuscript is well structured. The introductory paragraph is well designed, contextualizing the topic discussed in the article. The concluding paragraph summarizes well the aspects addressed and the intention of the authors. The figures were well chosen and are important for comprehension.

I have some suggestions and questions. Initially, the authors show that continued high levels inflammation, above the levels of "good inflammation", correlates with the symptomatic presentation of AD. Then they say that this inflammation is mediated by TLR2/4 that activates NFkB.

But then when correlating the activation of these TLR2/4, this part of the text is a little confused. It would be natural a correlation between the continued activation of TLR/NFkB signaling with the accumulation of AB plaques in the symptomatic phase of AD. However, when describing studies, the manuscript often does not make clear the experimental context and the "disease stage" in which the damage related to TLRs is obtained, especially in the paragraph on page 4 (that starts in line 5). The phrase on line 10, may be addressing this issue of the TLR expression timeline, but it is not clear, it should be improved.

Thus, the review of these studies about TLR2 / 4 activation and correlation with A β accumulation and cognitive performance should be improved, mentioning the time window investigated. The end of this paragraph on page 4 (line 33) is summarizing well. But the reader should not wait until this moment to understand. The paragraph should be better contextualized from the beginning.

Final sentence of the paragraph (page 4 line 42) could be completed, saying that the administration of anti-inflammatory drugs should be before chronic phase and diagnosis of Alzheimer's disease through clinical presentation, and indicating to observe figure 1.

In conclusion paragraph (line 26), authors mention that a global inhibition of inflammatory signalling during the acute phase might be ineffective. They should complete this information pointing here also that NSAIDs treatment on the elderly was not effective either, as explained in the third paragraph.

Figures 1 and 2 are changed in order. Figure 1 must be 2, and figure 2 must be 1.

And a final suggestion: one question is raised in reading the manuscript, how to identify correctly the brain inflammatory status in order to propose a correct time for inflammatory drugs treatment, since AD is diagnosed after that therapeutic window? How to identify individuals that will be in the future diagnosed with AD? Are there pre-clinical aspects that can be detected? It would be very interesting to have this question discussed in the text.