Reviewer's report

Title: Adjuvant TACE inhibitor treatment improves the outcome of TLR2-/- mice with experimental pneumococcal meningitis

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Reviewer: Annamaria AV vezzani

Reviewer's report:

General
This manuscript describes the effect of a TACE inhibitor alone and in association with an antibiotic on disease progression and survival rate in mice infected with Streptococcus Pneumoniae representing a model of meningitis. The authors used in this study mice lacking TL2R and/or CD14. In these mice they measured TNF in CSF and bacterial number in CSF and brain.

They conclude that the combination of TACE inhibitor and antibiotic is more effective in rescuing a higher % of TLR2 KO mice than either one alone.

This manuscript reports some novel evidence and several findings already published by the authors in their previous papers or by other groups in the literature.

The novel part of this work is related to the use, and the “therapeutic” effect, of the combined treatment of antibiotic and TACE inhibitor in TLR2 KO mice. Emphasis should be given that this is the novel aspect of this study. As it stands now, the authors mixed the novel evidence and the already published findings throughout the text.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The findings already established in previous publications appear to be the following:

1. accelerated mortality of TLR2 and CD14 KO mice infected with S.P.
2. Early death associated with high bacterial load in these KO mice
3. Excess TNF-alpha in CSF in these KO mice
4. Efficacy of antibiotic or TACE inhibitor treatment on S.P.-induced experimental meningitis in otherwise normal mice

These data are presented in the figures of this manuscript as a comparison with novel data related to the use of double KO mice. However, the double KO mice have not been used for the pharmacological experiments where only TLR2 and CD14 KO were studied. Therefore, I suggest that the data shown in figure 1 and 2 should be deleted and simply mentioned in the text.

Alternatively, Figure 2 as it stands now shows bacterial load (A) and TNF measurements (B) in the total population of mice. However, one can deduce from Fig 1 panel A that only part of the mice show the high severity score particularly after 24 h. To link bacterial load and high TNF in CSF to disease progression it would be important to divide the measurements of these 2 parameters in the 2 population of mice, namely the ones developing an accelerated disease progression vs the others. As presented now these data do not appear to explain the changes in mice behavior after infection or the success of the treatments. The data on the effects of treatments alone or in combination on these parameters should be shown in one figure or table since they are instrumental for explaining the better outcome of the combined treatment.

It is not clear why the authors used TLR2 and CD14 KO mice: is it to mimick a more severe condition of bacterial meningitis? Does disease severity differ in humans? Do the author wish to suggest that a TLR2 mimick would improve the therapy in this pathological condition? These aspects should be clearly defined in the Introduction and aims.

The differences between TLR2 and TLR2/CD14 KO mice should be explained more convincingly. I would expect to find the effects observed in TLR2 KO mice potentiated in double KO mice.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Why the treatments were stopped after 4 or 5 days while mice were observed for 9 days? Why the antibiotic treatment was longer than TACE inhibitor treatment?

How motor activity was assessed in mice?
Were the mice killed at the various times indicated AFTER S.P. inoculation? Please clarify (p. 7, line 6).

In general, the number of mice used in each experiment in the various exp groups should be reportd in the method section.

Statement in Discussion at p. 12, line 10 are not supported by the data since double KO mice have the same rate of survival as CD14 KO mice but they do not show any increae in TNF alpha.

Fig 1 panel C should report that antibiotic was administered.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No