Author's response to reviews

Title: Non-neuronal and neuronal BACE1 elevation in association with angiopathic and leptomeningeal beta-amyloid deposition in the human brain

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Version: 2
Date: 26 February 2015

Author's response to reviews: see over
Responses to Reviewer’s reports

Reviewer’s report
Title: Non-neuronal and neuronal BACE1 elevation in association with angiopathic and leptomeningeal beta-amyloid deposition in the human brain
Version: 1  Date: 31 January 2015
Reviewer: Roxana R Carare

Reviewer’s report: In this paper, authors describe an increased expression of BACE1 in capillaries, arterioles in cases of CAA, complementing the recent findings that demonstrate BACE in isolated leptomeningeal vessels from cases of CAA (1).

The novel and interesting aspects of this paper lie in demonstrating the expression of BACE1 in in cultures of human vessels, meningeal cells and at the level of pia mater. I have no major concerns and recommend publication after minor essential revisions including careful proof reading as there are some grammatical errors. I would also recommend inserting the following into the discussion:

The results may be relevant in the clearance of Aβ along perivascular drainage pathways, as the leptomeningeal vessels posess a layer of leptomeninges as an adventitia (2, 3). Increased expression of BACE1 of the endothelial cells may result in further problems with the clearance of Aβ, already compromised due to age (4) The findings also correlate with experimental data that demonstrate that APPDutch mice crossed with BACE1 tg mice display more CAA with regional preferred distribution (5).

References

Responses: We thank the reviewer for providing the references and the excellent suggestion to relate our work with previous studies in a broader context. Certainly this would extend a much better background to the readers. We have cited these papers and findings in the introduction (the second paragraph).

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published.

Responses: Agreed. We have thoroughly re-edited the manuscript.
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.
Dr. Zhi-Qin Xue, et al reported that BACE1 elevation in the endothelia and perivascular neurites involved in angiopathic Aβ deposition, while BACE1 elevation in meningeal cells contributed Aβ to leptomeningeal amyloidosis. BACE1 immunoreactivity (IR) increased locally at capillaries, arterioles and along the pia, localizing to endothelia, perivascular dystrophic neurites and meningeal cells, and coexisting with vascular iron deposition. The expression of BACE1 and other amyloidogenic proteins in the endothelial and meningeal cells also occurred in primary cultures prepared from human leptomeningeal and arteriolar biopsies.

1. As the control and dementia of the AD or vascular type are aged individuals, the final neuropathological diagnosis for the brains used in the study is important.

Response: We appreciate this comment.

2. BACE1-IR at capillary and arteriole-like profiles was confirmed by double immunofluorescence for BACE1/6E10 (Fig. 1K-N) and BACE1/collagen IV (Fig. 2A, B). It is important to show BACE1 and beta-amyloid (6E10) in endothelial cell, or just in the perivascular area.

Response: Appreciate the comment.

3. Small arteries and leptomeningeal samples are from leptomeningeal biopsy. Please indicate the amount of samples for western blot analysis in figure 5F.

Response: Provided in the figure legend.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.
Response: We appreciate the evaluation by the review on our work.
Declaration of competing interests: I declare that I have no competing interests

Response: We thank the reviewer for the evaluation and considering that this work “will be of wide interest to researchers (both basic and clinical) in the field of neurodegenerative disease”.