OPEN PEER REVIEW REPORT 1

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Title: Could autophagy dysregulation link neurotropic viruses to Alzheimer's disease?
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COMMENTS TO AUTHORS

In this review authors analyse the link between viral infections and the development of neurodegenerative disease. The link seems to be the alteration in autophagy. Viruses can block or alter the autophagic processes. Autophagic processes alterations are in the base of the intracellular accumulation of amyloid peptide and hyperphosphorilated tau that induces cell death and subsequent extracellular amyloid plaques formation thus are responsible to the onset and progression of neurodegenerative diseases such Alzheimer's disease.
The review is very interesting and well-written and present clear evidences for the possible link between virus infection and AD progression. This review opens a new line of evidence that could give interesting clues for the study of neurodegenerative diseases and allow in the future the development of alternative therapies to the treatment of these diseases.
I have a couple of suggestion that, in my opinion, could improve the quality and interest of the review.

First of all, analyzing the autophagy in AD, it has been observed the presence of intracellular deposits of lipofuscin in neurons from adult and old humans. It will be interesting to mentioned it and to include some information about this accumulation and its relation with aging and AD. It exists any relation between these lipofuscin granule accumulation and the bad processing of amyloid or tau peptides?. Neurons from AD patients present an excess of autophagosomes, but they can be also found in old individuals without AD. Could be concluded that AD is just an accelerated process of accumulation of autophagosomes and in a way an accelerated aging process?.

There is a very interesting point, herpesviruses can block or modify autophagic processes in order to accomplish their own formation and the progression of infection. In some cases these alterations are fully known and affected specific proteins. Several studies have demonstrated that the presence of certain herpesviruses can interact with the amyloid peptide processing and subsequent deposition. It has been observed a high concentration of some herpesviruses in the brain of patients suffering AD. More interestingly is the link between HHV-6 virus and microglia. This virus is able to infect and activate microglia increasing inflammatory response that is one of the hallmarks of AD. It will be interesting to amplify this point in the review.