Reviewer's report

Title: GDNF protects apoptosis in enteric glia: Evidence for an autocrine loop

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Reviewer: Bindu Chandrasekharan

Reviewer's report:

The authors Steinkamp et al in their article ‘GDNF protects apoptosis in enteric glia: Evidence for an autocrine loop’ aims to unravel the role of a neurotrophin-glial derived neurotrophic factor (GDNF) in the regulation of enteric glial apoptosis. The authors observed GDNF and apoptosis marker (caspase3/7) in the biopsy specimens of Crohn’s disease patients by immunofluorescence. In vitro studies on enteric glial cultures (EGC) revealed that the combination of IFN-# and TNF-# induced apoptosis, but addition of GDNF to the culture does not affect the amount of apoptosis. However, neutralization of GDNF in the EGC cultures dramatically increased apoptosis in these cells. The authors claim that as enteric glia produce high amounts of GDNF during inflammation, their results suggest an autocrine apoptosis protection loop in these cells in CD.

The manuscript needs following revisions before publication.

Major compulsory revisions

1. The authors have shown GFAP/ Caspase-3/7 merge staining and GFAP/GDNF merge staining in biopsies. It would be interesting to check if GDNF positive tissue is positive for caspase-3/7 and this result would add to the conclusions.

2. Have authors looked at expression of GDNF receptors (GFR and Ret) in the Crohn’s patient biopsies-is there an upregulation?

3. The authors demonstrated that addition of anti-GDNF antibody increases the extent of apoptosis induced by a combination of TNF and IFN. Is this true for other cytokines like IL-1B or IL-6 on glial apoptosis. The authors could try a combination of pro-inflammatory cytokines (TNF+ IL-6 + IL-1B) and validate their result with anti-GDNF antibody.

4. The enteric glial cell apoptosis has been demonstrated by caspase3/7 staining, have authors looked at glial cell proliferation in the biopsies staining and in vitro cultures by Ki 67 or BrDU staining. This would help assess if increased apoptosis is related to decrease in cellular proliferation or an effect of GDNF in itself.

Minor revision

5. The conclusion part of the manuscript seems to reiterate the results, authors could cite more relevant references and compare and discuss their results.
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