

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-21-00910

Title: Translation stalling and ribosome collision leading to proteostasis failure: implications for neurodegenerative diseases

Reviewer's Name: Xinjie Chen

Reviewer's country: USA

COMMENTS TO AUTHORS

This is an interesting, timely and well written Perspective summarizing recent findings supporting a link between protein translation stalling and neurodegenerative diseases including Parkinson's disease, ALS and AD. The author explained the importance of the ribosome-associated quality control (RQC) mechanism that is required for handling translation stalling, and the consequences of defective RQC including CAT-tail formation that challenges global proteostasis and potentially, causes mitochondrial dysfunction. I have a few suggestions as listed below.

- 1) The section dealing with PD and PINK 1 reads unfinished. I understand that CAT-tailing occurs on specific mitochondrial proteins in cells lacking PINK1. It would be helpful if the author comes back at the end of this section to stipulate what exactly PINK1 is doing in preventing CAT-tailing in contrast to its suggested role in mitophagy.
- 2) Although the author described the CAT-tailing of specific mitochondrial proteins and targeting of CAT-tailed proteins into mitochondria, it is unclear how mitochondrial homeostasis and function (page 6, and Figure 1) are affected. Are there any direct evidence to support these claims? If yes, it would be good to have this included. If not, the author may need to rephrase it in the manuscript.

Minor comments:

- 1) Page 1, line 28: why "cellular co-factors"?
- 2) Page 2, line 15: "faulty"
- 3) Page 2, line 48: it would help if the author defines the molecular nature of ABCE1.
- 4) Page 3: the standard 3-letter codes should be used to describe the amino acids.
- 5) Page 4, line 30: delete "." After poly(GR).
- 6) Page 4, line 40: "negatively charged"
- 7) Page 5, line 16: beta-amyloid