

## OPEN PEER REVIEW REPORT 1

**Name of journal:** Neural Regeneration Research

**Manuscript NO:** NRR-D-19-00321

**Title:** Axon regeneration induced by environmental enrichment – epigenetic mechanisms

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**Reviewer's country:** United Kingdom

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### COMMENTS TO AUTHORS

In the article entitled "Axon regeneration induced by environmental enrichment - epigenetic mechanisms," the authors provide a current overview of recent work demonstrating the effect of EE on axon regeneration. In the article, they discuss the regeneration observed with EE in the context of spinal cord injury as well as sciatic nerve injury. They go on to discuss candidate mechanisms for this enhanced repair included enhancement of CBP (CREB-binding protein) activity. They continue this discussion with an overview of modulation of DNA methylation and its effects on axon regeneration.

This article is a timely, well-written perspective on the role of epigenetic mechanisms in axon regeneration as evidenced through EE experiments as well as others. It provides good insight which I think will be useful for the field of neuroregeneration.

I only have a few minor comments to be addressed:

-In the first paragraph, there is a statement "..., and PTEN deletion or silencing is thus invariably favorable for regeneration." There are no references for the statement. A reference to Park et al., or Liu et al., or any of the associated reviews published by that group should be included here.

-The figure provides a nice overview to the Perspective topic, however with regard to the box showing intranuclear CBP activation as a result of EE, is this oversimplified? It reflects the discussion in the review, but is it known that the EE-induced activation of CBP is direct, or are there any upstream molecules that could also be involved that could be considered to be included in the figure? cAMP? CREB?