OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00084
Title: Membrane progesterone receptors (mPRs/PAQRs) in Schwann cells represent a promising target for the promotion of neuroregeneration
Reviewer's Name: Yuanquan Song
Reviewer's country: USA
Date sent for review: 2020-2-24

COMMENTS TO AUTHORS

The manuscript "Membrane progesterone receptors (mPRs/PAQRs) in Schwann cells represent a promising target for the promotion of neuroregeneration" reviewed the potential role of schwann cell progestogens and mPRs during neuroregeneration, based on the literature and the authors own recent findings. Overall, the authors did a fantastic job summarizing the role of schwann cells in neuroregeneration, and provided a reasonable rationale why the progestogens and mPRs may serve as potential targets for promoting neuroregeneration. They have also delineated the possible mechanisms, through which the schwann cell progesterone receptors may impact neuroregeneration.

Main points:

1. The strength of the manuscript lies in the authors' clear depiction of their recent findings, investigating into the role of progestogens and mPRs in schwann cell physiology. This makes a strong case that the relevant pathways may have a beneficial effect in peripheral neuroregeneration. However, it needs to be pointed out that while it is perfectly reasonable to hypothesize that these pathways may regulate neuroregeneration, there is really no direct evidence so far, reporting a regeneration phenotype when the pathways are manipulated. Some of the writings appear to suggest that they are known to regulate regeneration.
2. The proposition on CNS regeneration, however, seems to be a weak case. For example, when they were discussing "Can mPRs be relevant in promoting spinal cord regeneration?", all they mentioned was just schwann cells, which doesn't seem to be much involved in CNS regeneration under physiological conditions. Here seems to be the logic presented by the authors: mPRs activation downregulates MAG and MAG is reported to inhibit schwann migration; therefore, mPRs can promote Schwann cells migration in to the spinal cord and promote regeneration. Alternatively, manipulating mPRs may help the migration of schwann cells when transplanted into the spinal cord. These are definitely possible, but feel a bit far-fetching given the available data and the literature. It is a bit hard to justify that "mPR activation would be a promising target for the regeneration of both the peripheral nerves and the spinal cord", especially in the spinal cord. This is the main weakness of this manuscript, although it's understandable as the literature on mPRs and neuroregeneration is limited. Maybe discussing more about schwanns and regeneration, and more details of their findings which can be linked to known facts of schwanns/regeneration would be helpful. Also maybe expand a bit on the schwann cell transplantation strategy.
3. The authors found that mPRs activation leads to cAMP downregulation which then promotes schwann cells proliferation. On the other hand, there are studies demonstrating that cAMP elevation regulates proliferation of schwann cells. This should be discussed in more detail.

Minor concerns:

1. P.1 37-38, it should be "presence of schwann cells in the central nervous system".
2. P. 3 53, it should be "downstream of mPR activation".

OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00084
Title: Membrane progesterone receptors (mPRs/PAQRs) in Schwann cells represent a promising target for the promotion of neuroregeneration
Reviewer's Name: Dengbing Yao
Reviewer's country: China
Date sent for review: 2020-3-4

COMMENTS TO AUTHORS

As stated in the manuscript title, this paper tries to hypothesize mPRs/PAQRs in Schwann cells represent a promising target for the promotion of neuroregeneration. In this paper, the authors hypothesized the role of progestogens and mPRs in the promotion of nerve regeneration, described pro-regenerative effects of progestogen treatment, and in particular of mPR activation, in Schwann cells. The contribution of Schwann cells to the regeneration process after nerve injury is very large. However, the precise molecular mechanism(s) which regulates Schwann cell function remains unclear. Nerve repair is a result of activated regeneration in relation with newly activated injury dependent process. Regeneration was regulated initially following nerve injury and repair and the injury-induced switch to the genetic response also featured a number of degeneration and regeneration-specific genes. During the period of nerve injury, the morphological changes of Schwann cells are likely to be mediated by the actin cytoskeleton, which play a key role in cell shape changes in response to various stimuli. The Schwann cells take the major role in myelin cleaning and proliferation. Schwann cells have been observed to recruit macrophages by release of cytokines and chemokines after nerve injury. The proliferation could further enhance the myelin cleaning rates and plays an essential role in regeneration. The fact that many gene differential expressed indicated that sustained regulation at consecutive time point means executed regenerating/repairing by a continuously progressing program. One of the major Schwann cell responses after nerve injury is its dedifferentiation, proliferation, and redifferentiation.