OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00424
Title: Dynamic glial response and crosstalk in demyelinationremyelination and neurodegeneration processes
Reviewer's Name: Tetsuya Akaishi
Reviewer's country: Japan

COMMENTS TO AUTHORS

In this article, cellular and molecular interaction between glial cells during the demyelination-remyelination process in MS lesions, centering OPCs/OLs evolution, is reviewed.
The manuscript is well written and well organized with profitable figures and tables.
I have only several minor comments.

1. Page 4: "Astrocytes compromise 80% of the total glial cell population in adult CNS (Verkhratsky and Butt, 2007)."
The term "compromise" seems not to be appropriate. "Comprise" might be better.

2. Page 7: "... , suggesting that individual variability and extent of remyelination must be considered in developing therapeutic strategies for MS (Patrikios et al., 2006).
The term "must" may be better to be weakened to "should".

3. Page 9: The sentence "M/M are highly responsive active sensors that damage or insult by antigen presentation and phagocytosis." is hard to understand. Could this part be rephrased?

4. Page 13: "Patterns of astrocyte-derived factors and the switch of astrocytic phenotypes from A1 to A2 during lesion development indicate that finely regulated and balanced astrogliosis may benefit remyelination (Haindl et al., 2019)"
Please spefify or define the "A1" and "A2" in their first appearance. Maybe, toxic reactive astrocyte (A1) and neuroprotective reactive astrocyte (A2)?

OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00424
Title: Dynamic glial response and crosstalk in demyelination-remyelination and neurodegeneration processes
Reviewer's Name: Anna Maria Colangelo
Reviewer's country: Italy

COMMENTS TO AUTHORS

This report summarizes current knowledge of the complex interplay between glial elements (microglia, astrocytes and oligodendrocytes) linked to neuroinflammation and demyelination/remyelination processes in models of Multiple Sclerosis. The authors provide an accurate overview of the cellular and molecular events, such as release of specific cytokines and growth factors, modulation of ECM and signaling pathways affecting OPC differentiation, which can be considered as specific therapeutic targets at specific phases of the disease and plaques.

The report is well structured. Tables are very clear and useful, as they provide a schematic overview of plaques classifications, their cellular components, specific markers and related references.

Some minor revisions:

The authors need to reword the sentences reported below, which are not completely clear.

Page 9 lines 210-211 - M/M are highly responsive active sensors that damage or insult by antigen presentation and phagocytosis.

Page 9 lines 212 - reactive oxygen species. It might be useful to add the acronym and use it in the next part of the text

Page 15 lines 346-348 - Evidence shows it is not the lack of OPC population in the plaques but insufficient OPC recruitment and differentiation that are limiting steps for remyelination (Boyd et al., 2013).

Page 16 lines 357-358 - Reactive astrocytes (GFAP+) improve myelin debris clearance to allow proper remyelination by secreting CCL2 and CXCL10 to recruit and active M/M (RCA-1, Mac-3+, Iba1+, MHC II+).

OPEN PEER REVIEW REPORT 3

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00424
Title: Dynamic glial response and crosstalk in demyelination-remyelination and neurodegeneration processes
Reviewer's Name: Olga Chechneva
Reviewer's country: USA

COMMENTS TO AUTHORS

The review covers the data related to the behavior and function of glial cells in neuroinflammation associated with demyelination. In general, the idea is interesting and includes the data from animal and human studies.

Major points:

1. The paper is composed of the published facts without much interpretation and conclusions. Often the facts are not logically linked to each other and do not lead to the specific point that makes it difficult to follow.
2. Macrophages are not glial cells. Their role in inflammation in MS should be differentiated from microglia.
3. Many facts are not clear presented, for ex. The differences in function between M1 and M2 microglia.

Minor points:

4. Table 2: information is summarized in the text and do not need to be organized in the separated Table.
5. Table 3: too much information. The information presented in the Table is lacking compactness/specificity.