Journal of Neurotrauma
04-Jun-2012

Dear Dr. Ibarra:

Manuscript ID NEU-2012-2501 entitled "BCMA, APRIL and BAFF are candidate mediators of SCI-induced autoimmunity" with Dr. morse as contact author has been submitted to Journal of Neurotrauma.

I invite you to review this manuscript. The abstract appears at the end of this letter, along with the names of the authors. Please let me know as soon as possible if you will be able to accept my invitation to review.

If you are unable to review at this time, we would appreciate you recommending another expert reviewer by emailing jtpovlis@vcu.edu.

You may click the appropriate link at the bottom of the page to automatically register your reply with our online manuscript submission and review system. PLEASE DO NOT RESPOND TO THIS EMAIL.

Once you accept my invitation to review this manuscript, you will be notified via e-mail about how to access Manuscript Central, our online manuscript submission and review system. You will then have access to the manuscript and reviewer instructions in your Reviewer Center.

I realize that our expert reviewers greatly contribute to the high standards of the Journal, and I thank you for your present and/or future participation.

Sincerely,
Dr. W. Dalton Dietrich
Journal of Neurotrauma Editorial Office

Comments to the manuscript

The manuscript entitled “BCMA, APRIL, and BAFF are candidate mediators of SCI-induced autoimmunity” by Saltzman J *et al*, explores the molecular signaling pathways and mechanisms by which autoimmunity is induced after spinal cord injury (SCI). The final goal was to identify potential targets for therapies that would reduce tissue damage and inflammation in chronic stages of SCI. For this purpose, Saltzman and co-workers performed a microarray analysis of circulating mononuclear cells in order to identify which genes are differentially expressed. They found 1970 genes from which 1453 were identified by IPA software to be present in 25 molecular pathways. The authors selected a single network which functions include lymphoid tissue structure and development. From this network, BCMA, APRIL and BAFF were upregulated and were therefore selected to be analyzed using quantitative PCR. The previous genes were all found to be upregulated in mononuclear cells. Therefore the authors finally concluded that SCI autoimmunity is regulated via APRIL and BAFF by activating B cells through BMCA. Before speaking about some punctual observations, I would like to comment that autoimmunity does not depend only on B cell activation. Autoimmunity is a more complex phenomenon which includes innate and adaptive (T cell) immune system activation. Hypothetically, even activation of B cells (those that could promote autoimmune disease), depends on T cell activation. Therefore, we could not asseverate that SCI autoimmunity is regulated only by B cells.

Although the findings seem to be interesting, there are some major and minor issues that must be clarified or carried out before it can be considered for publication.

Major issues:

1. I have an important concern regarding the number of individuals used for this study, it is quite small (6 for SCI and only 5 healthy patients). I am sure that the size of the sample is not truthfully representative even for an exploratory study. Therefore it is difficult to consider any solid conclusion. In order to reinforce the results I recommend increasing the number of patients.

2. Throughout the manuscript the authors claim that the analysis of genes was performed in monocytes. With this regard, there is an important misconception. Authors obtained mononuclear cells from peripheral blood. The Histopaque technique isolates leukocytes and not only monocytes. There is no evidence in the manuscript demonstrating that the authors purified monocytes.

3. If the authors found 25 molecular pathways with differentially expressed genes, why did they only analyze the one with BMCA, BAFF and APRIL genes. B lymphocytes are not the only cells implicated in autoimmunity. Authors should clarify this issue in the manuscript.

4. The discussion on the role of B cells in SCI is mainly based on the results of one laboratory (Dr. P. Popovich lab). The function of B cells after SCI and autoimmunity against myelin basic protein (MBP) in chronic SCI patients has also been described by other authors (Schori H et al., J Immunol 2007, 178(1), 163-171; Schori H etal, J Immunol 2002, 169(6), 2861-5; Zajarias-Fainsod D et al., Eur Spine J 2012, 21(5), 964-70). I recommend reading and including these into the discussion section. Aside from this, authors should discuss the beneficial role that autoimmunity could play after injury even in the chronic stages of SCI. The latter is important since the scientific data has provided realistic evidence on the favorable action of this immune response after injury.

5. In the discussion section the authors suggest that activated B cells secrete autoantibodies that contribute to tissue damage and neurotoxicity after SCI. At the moment this issue has not been clearly demonstrated. According to existing findings, the role of autoantibodies is very controversial and not conclusive. Despite previous studies that reported harmful effects (Ankeny 2006), others, did not demonstrate any damage induced by these autoantibodies; moreover, it has been shown that, the same autoantibodies , are also detected before injury (Ibarra A et al. Neuroscience 2000, 96(1), 3-5). Additionally, a recent study demonstrated the presence of specific MBP-IgG antibodies in patients with chronic SCI (> 10 years). One of the relevant findings of this study was that, despite autorreactivity, no significant change in neurological impairment was evident in SCI patients. Furthermore, the response to MBP was higher in patients with incomplete (AIS B) than those with complete impairment (AIS A) (Zajarias-Fainsod D et al. Eur Spine J 2012, 21, 964-70). Therefore, we cannot asseverate that these autoantibodies are necessarily harmful. I recommend the detailed review of these articles and their further discussion in the manuscript.

Minor issues:

1. Authors should include more recent studies on the autorreactive response in patients with chronic SCI. For instance, a recent publication was not included (Zajarias-Fainsod, Eur Spine J 2012, 21, 964-70).
2. The mechanism of injury for each patient should be included.
3. In the Results section change ASIA to AIS, this is the proper abbreviation.
4. In Methods section, qPCR: More information is needed as to understand how the authors obtained the final results. For instance, melting temperatures are not mentioned; which gene was used to normalize the values? etc.

COMMENTS TO THE EDITOR

The manuscript is not conclusive, especially because of the number of individuals used for the study. I do not recommend the publication of this manuscript in its present version.

20-Jun-2012

Dear Dr. Ibarra:

Thank you for reviewing manuscript # NEU-2012-2501 entitled "BCMA, APRIL and BAFF are candidate mediators of SCI-induced autoimmunity" for Journal of Neurotrauma.

Once a decision on this manuscript has been made you will be able to view the decision letter by logging into your reviewer center.

On behalf of the Editors of Journal of Neurotrauma, we appreciate the voluntary contribution that each reviewer gives to the Journal. We thank you for your participation in the online review process and hope that we may call upon you again to review future manuscripts.

Sincerely,

Dr. W. Dalton Dietrich
Editor, Journal of Neurotrauma
ddietrich@miami.edu, HBramlett@med.miami.edu