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Response to Reviewers

Dear Editor,

Please find below our comments and replies to the referee's comments regarding the manuscript #19846, entitled "RNA-binding proteins related to stress response and differentiation in protozoa" submitted to The World Journal of Biological Chemistry. We wish to thank the referees for their suggestions and criticisms that helped to improve the manuscript.

Reviewer 00467115

Alves and Goldenberg review in their article RBPs in protozoa with an emphasis on stress response and differentiation. In the first part they give very brief summaries of some of the domains commonly found in RBPs, however these are far too short in order to give the reader any clear picture. Thus, for example, the authors do not really make clear why RBPs need in addition to the RBD and RRM – and what the functional difference between the two is.

Response: The first part of the review was intended to be short, is for the reader to be informed about the main domains that will be cited throughout the review. If any specific domain needs to be further explored by the reader it is possible to go after the reference. RBD means RNA Binding Domains and includes all the domains found in RBPs such as RRM, CCCH, KH, etc.

A figure of a "typical" RBP with its domains and their functions would be very helpful.

Response: There is no "typical" RBP as it has been shown the great variety of the domains that be found and also the combination of different RBDs that are present in a RBP. Therefore as the intention of the review was to describe the function of the RBPs in protozoa and not to discuss their structure we think it is not necessary to add any particular scheme of RBPs.

Unfortunately the second part (RBPs in protozoa) again reads more like a list than like an article. In the present form, not much would be lost by shortening this chapter to the last paragraph – as the table provides most of the information of the chapter. However, this chapter should be considerably extended to a critical review of the literature. It is somewhat confusing that the authors chose many examples from the vertebrate world – why, for example MDM2 as an example for alternative

splicing when the article concerns protozoa? In general, this review has potential but should be much more detailed and critical.

Response: All the data available in the literature regarding RBPs in protozoa has been covered in this review as a list or as a description of their function. In our opinion it would be tiresome for the reader if we added complete information about each protein characterization.

We agree with the reviewer and removed the examples of RBPs in differentiation in metazoan.

minor issues: line 140: formatting problem. line 145: With regard to splicing line 248: cases line 268: cytochrome C is not a complex!

Response: The minor issues pointed by the referee have been corrected.

Reviewer 00609371

This article reviewed and updated the roles of RNA-binding proteins (RBPs) in the cellular response to physiological stress, in cell differentiation, and in the cellular localization of certain mRNAs, especially in Trypanosoma. Generally speaking, this is a concise and fairly well-written manuscript that covered a quite a few important yet underappreciated areas. However, I believe this article could be better if the following issues are appropriated addressed:

1) General introduction is absent.

Response: The intention of the first part of the review was to provide a clear and simple picture of the RBPs and the main domains found in these proteins. Consequently we did not want to expand this part leaving to the reader the option to search for the references mentioned in the review.

2) Even though the 1st subtitle is "RNA-binding proteins", the most part was actually devoted to discussion the different domains of RNA-binding proteins, therefore the subtitle need to be modified to reflect the content.

Response: We agree with the reviewer and changed the subtitle accordingly.

3) Figure 1 is oversimplified to be useful. The authors need to add more details, such as P body and stress granules, to appropriately reflect the current understanding of the field.

Response: We modified the figure in order to include stress granules and p-bodies, even though in parasites they might be less complex than in metazoan.

Typo: "139 cell survival. For example, a 43-kDa protein takes 0.625 seconds to diffuse a distance of 10 ?m[46]

Response: We corrected the text.

Reviewer 00338280

Comments: In this manuscript, Alves and Goldenberg reviewed published studies on the roles of RNA binding proteins in stress response and differentiation. Previous studies have demonstrated that, through specific association with RNA, the RNA binding proteins regulate the function and fate of RNA molecules. Overall the review provides collective information into the mechanisms of RNA binding protein. Given the importance of RNA binding protein in human disease, the topic is of general interest. The manuscript is well written. However, the manuscript suffers from deficits that need to be carefully addressed. The authors should have added their comments to the related studies, rather than just to pile up the published studies.

Response: This field is relatively new in protozoa. Consequently there are few data and they are not conflicting to justify or substantiate conjectures or opinions. The idea of this review was to provide a state-of-the art.

The audience would look for deeper mechanisms for RNA binding protein functions. The opinion from the authors is very important. The authors may want to expand the section for the important roles for RNA binding protein functions during stress response, because this is supposed to be the major topic of the review.

Response: We agree with the reviewer; however, mentioned above as all the RBPs related to stress in protozoa have been discussed. The connection between stress, differentiation and RBPs is emerging in parasitic protozoa, especially the RNA regulon theory, evidencing the importance of the RBPs in stress response.

Reviewer 00541708

The authors provide a high quality review on the role of RNA binding protein in the context of stress and differentiation in protozoa. The review is well written and raised main questions and perspectives in the research field.

Response: We than the referee for the positive comments.

Finally, we wish to thank you for your care and attention in handling this manuscript and we hope it can be accepted for publication on its present form.

Yours sincerely,

Samuel Goldenberg