

### **Response to reviewers:**

**Reviewer 1 (ID 03798488):** In this manuscript, Carlos Pascual-Caro and colleagues investigate STIM1, a transmembrane protein of the endoplasmic reticulum with a key role in  $\text{Ca}^{2+}$  mobilization emphasizing the role in neurodegenerative diseases. I think that some adjustments are required to substantially improve the manuscript and make it acceptable for publication. The following main points should be addressed:

- Page 3 section “STIM1 AND CALCIUM MOBILIZATION”: lines 40-50 should be rewritten. Indeed, it is not clear how STIM1, a transmembrane protein of the endoplasmic reticulum can increase the cytosol and/or the extracellular  $\text{Ca}^{2+}$  concentration. Explain better or integrate with the next paragraph;
- Page 6 section “STIM1 IN NEURONAL CELL DEATH”: lines 134-136 it would be appropriate to extend the argument to ROS-induced ROS release. Moreover, it would be appropriate to discuss about the role of the mitochondrial permeability transition pore when the  $\text{Ca}^{2+}$  concentration suddenly increases in mitochondria; In addition, in my opinion the inclusion of some figures would make the reading of the review more engaging.

### **Response to Reviewer 1:**

We thank the reviewer for his/her helpful suggestions. Following these suggestions we have re-written the paragraphs under the heading “STIM1 AND CALCIUM MOBILIZATION”.

Following reviewer’s suggestion we have extended the discussion of the role of ROS in the “STIM1 IN NEURONAL CELL DEATH” section (previous lines 134-136).

Finally, we have included a final figure with the more important findings reviewed in our manuscript.

**Reviewer 2 (ID 02620433):** In the minireview “The role of STIM1 in neurodegeneration” by Pascual-Caro et al., an attempt to briefly summarize the data about the participation of STIM1 in neurodegeneration was undertaken. It should be mentioned that several “full-bodied” reviews addressing this problem in details appeared recently [1-5]. Although some of them [1-2] appeared three years ago and are in open access, they are not mentioned by the authors. I understand that minireviews are very important publications, however, to my mind they should address either quite recent finding in the field or discuss the general problems, developments and prospects without going in very details which are already addressed in reviews...

**Reply:** Because this is a minireview, we focused the manuscript on recent aspects of STIM1 and neurodegeneration, rather than addressing all the aspects of the pathophysiological role of STIM1 in neurons. However, following a classical distribution of the information in any review, we first introduced these findings by describing general aspects of STIM1 function, without going onto details. Thus, the article could be much more attractive for potential readers, as any Editor would expect from a minireview.

Regarding the already published reviews, we would like to give our personal point of view. The San Francisco Declaration on Research Assessment (DORA), which has been signed by many individuals as well as international recognized academic institutions, publishers, etc., suggests that “Wherever appropriate, (researchers should) cite primary literature in which observations are first reported rather than reviews in order to give credit where credit is due”. We strongly believe in this, and we always try to give credit to the original reports. Accordingly, we always keep the number of cited reviews to the minimum, as we did in this case. In addition, citing previous reviews in a mini-review does not look to be a good strategy to discuss previous findings. In conclusion, although we believe that the reviews mentioned by the reviewer are excellent piece of work, there are no reasons to cite them in this case.

**Reviewer 2:** The manuscript presentation is completely different from that accepted in the journal. It should be formatted according the Guidelines for Manuscript Preparation and Submission: Minireviews. The language should be greatly improved. In the present form sometimes, it is difficult to understand the idea of the authors. I strongly recommend to seek a help of native English-speaking person or use language editing service.

**Reply:** The manuscript has been formatted according to the Guidelines for Manuscript Preparation and Submission: Minireview. The original manuscript had been revised by an English speaker (Paul Kiely, who has been working for us in the last few years as a professional editor). In any case, the revised manuscript has also been reviewed by the aforementioned language editing service.

**Reviewer 2:** The lines 201-220 are not related to the topic of the manuscript.

**Reply:** Lines 201-220 of the original manuscript describe how the accumulation of amyloid peptides affects  $\text{Ca}^{2+}$  mobilization, and how this accumulation upregulated  $\text{Ca}^{2+}$  entry through Cav1.2 channels. Because Cav1.2 are tightly controlled by STIM1, and the deficiency of STIM1 has been described in Alzheimer's disease patients, we consider that this paragraph is closely related with this minireview, so we really would like to keep this paragraph as it is. In the case the reviewer request to remove it, we will ask the Editor-in-Chief to make a final decision.

**Reviewer 2:** Conclusions should be rewritten, clearly stating the role of STIM1 in the neurodegeneration.

**Reply:** We have re-written the section, following the suggestion of the reviewer.

**Reviewer 2:** The cartoon illustrating the STIM interactions would be very helpful for understanding these complicated processes.

**Reply:** A single figure has been added to the text to show the link between STIM1 and other molecules/complexes involved in neurodegeneration. We thank the reviewer for this suggestion.

**Reviewer 2:** Minor points: The abbreviations in the abstract should be deciphered. The abbreviations in the main text should be used according to the guidelines. Some abbreviations are introduced just for the single use.

**Reply:** SOCE has been deciphered in the abstract. Other abbreviations were removed if they were used just once.