**Dear Editor-in-Chief,**

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Vitiligo as a potential degenerative disease: from oxidative stress to cellular senescence” . Those comments were greatly valuable and significant for revising and improving this manuscript. We have carefully studied the reviewers’ comments, and we have accordingly applied revisions. All the changes have been highlighted in red in the revised version of the manuscript, and we hope that the revised version of the manuscript would be acceptable for publication in your prestigious journal. The reviewers’ comments have been replied one-by-one as follows:

**# Reviewer 1**

Wang & Li review the limited knowledge regarding the links between cellular senescence and the pathology of vitiligo. Overall this is a good review of the available literature and is fairly well written. My comments were as follows:

Major comments:

1. The principal concern that I have is that there is substantial overlap between senescence markers and markers of acute inflammation. For example,acutely activated immune cells produce many SASP proteins, activate ROS and MAPK, and upregulate p16. Given the links between vitiligo and the immune system, it would be useful to be somewhat more critical of the senescence work presented here, to discuss the possibility that these are not senescent cells at all, and to reflect on further experiments that would be more convincing. This is especially relevant for melanocytes, since fully differentiated cells are not highly replicative and may be difficult to distinguish from senescent cells in a lot of ways anyway.

**Response:**Thanks for your comment. In order to clarify the characteristics of SASP, the authors introduced SASP in more detail in lines 103 – 115. For more detailed modifications, see the section in manuscript red.

SASP is a characteristic secretory phenotype that occurs after cellular senescence and is significantly different from the acute inflammatory response process. The increased secretion phenotype of SASP caused by cellular senescence includes a series of cytokines such as proinflammatory cytokines (such as IL-1α, IL-1β, IL-6 and IL-8), growth factors (such as HGF, TGF-β and GM-CSF), chemokines (such as CXCL-1/3 and CXCL-10) and matrix remodeling enzymes (such as metalloproteinases). These factors cause cellular senescence to accumulate and show some necessary phenotypes to identify senescent cells. They include (1) cell cycle arrest in G1; (2) flattened, enlarged cell morphology; (3) positive SA-β-gal) staining; (4) SAHF; (5) telomere shortening; and (6) high expression of p16, p53, and p21 cell cycle suppressor genes. Therefore, the above multiple characteristics need to be considered to determine whether SASP is secreted by senescent cells.

2. It would be helpful to revise some of the sections to make it more clear which studies examined melanocytes or other skin cells, and which are basic senescence studies on other (possibly less relevant) cell types.

**Response:** Thanks a lot for your valuable comment. Further changes have been applied according to your comments The authors changed the relevant sections in a timely manner after receipt, such as the original 2. Melanocyte senescence was changed to 3,. Melanocyte senescence, while the original 2.1 Overview of cellular senescence was changed to 2. Overview of cellular senescence, see the red section of the manuscript for more detailed modifications.

**Minor comments:**

1. DDR is first used as an abbreviation at line 75, but is not defined until line 85.

**Response:**DNA repair damage is abbreviated as DDR (lines 77, 90)

2. MC (first use line 161), MCS (first use line 168), and MCSS (first use line 170) are not defined. These may all be referring to the same thing.

**Response:**MC, MCS and MCSS were all modified to melanocytes.

3. Please check capitalization, etc. for abbreviations. There are a number of “ros” instead of ROS (lines 69, 165, 187 were the ones that I found,but there may be others). Also, h2o2 and H2O2 are used in places instead of the proper formula with subscripts. CLP should be in caps on line 219.

**Response:**ROS (line 71,166,193),H2O2(line 59-60) and CLP（line 263）.Errors have been corrected and are flagged in the manuscript.

4. SAPS instead of SASP on line 35.

**Response:**The error has been corrected (line 36) and is flushed in the manuscript.

5. TAF (lines 137, 138) is not defined.

**Response:**The Tumor Angiogenesis Factor is abbreviated to TAF (line 156) and the error has been corrected and is flushed in the manuscript.

6.A couple of sentences near lines 190-196 seem to be incomplete or improperly arranged.

**Response:**The inappropriate sentence has been removed (lines 232-235, 245-250), the error has been corrected and is flagged in the manuscript.

**# Reviewer 2**

The authors summarized the potential roles of oxidative stress on melanocyte senescence and the possible underlying mechanisms. This offers new insights for further understanding the pathology of vitiligo. However, the manuscript needs to be revised as below:

1. In section 2.3, the authors discussed the impacts of melanocyte senescence on keratinocytes and fibroblasts. Senescent melanocytes cause the senescence of neighboring keratinocytes and fibroblasts. As the topic of this manuscript is focusing on vitiligo, it is then important to discuss how the senescent keratinocytes and fibroblasts, in turn, affect melanocytes and contribute to vitiligo.

**Response:** Thanks for your significant comment. In this paper, the authors focus on the effects of low concentrations of ROS on melanocyte senescence, and its effects on surrounding keratinocytes and fibroblasts through paracrine in vitiligo. We found by searching the literature that senescent keratinocytes and fibroblasts, are induced by SASP secreted by ROS-mediated melanocyte senescence, and there is a causal link between these two, therefore, we first introduced vitiligo melanocyte senescence in this paper, and then continued to introduce keratinocyte and fibroblast senescence.

2. The immune aspect of vitiligo also needs to be discussed. Oxidative stress not only directly attacks melanocytes, but also indirectly causes damage to melanocytes by affecting immune cells, such as activating the infiltration of CD8+ T cells. Therefore, do the immune cells trigger the senescence of melanocytes as well? Is this also contributing to vitiligo?

**Response:** Thanks a lot for your significant comment. The authors added the role of immune cells in skin cell senescence in Section 3.2. Further information can be found in the red section of the manuscript.

3. The writing of the manuscript needs to be carefully proofread. There are many formatting and typing errors. For example, many extra dots can be seen after citation “Victorelli S et al..[57]” “Nelson G and Razdan N et al..” “Victorelli et al.. [62]”

**Response:**The error has been corrected (lines 139, 165, 153) and is flagged in the manuscript.