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Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 23187

Manuscript Type: Review

Response to reviewers' comments:

Reviewer 1

The goal of this review article was to provide a comprehensive review of RB functions in stem cells and stem cell-like behaviors of cancer cells. It is a well written review covering most recent information. Under the title tumor cell fate, authors have discussed only lung, breast, prostate cancer and soft tissue sarcoma. Authors should add data regarding ovarian and endometrial cancers as well. Planarians and plant stem information about the role of RB in stem cells should be removed. Overall it is a good thorough review.

→ We are very much delighted to see this reviewer's high evaluation. According to this reviewer's suggestion, we have extensively surveyed literatures that describe the RB function in tumor cell fate of particularly ovarian and endometrial cancers, however, unfortunately, we finally failed to find appropriate information regarding these types of tumor. Therefore, we could not load new information regarding ovarian and endometrial cancers.

→ This reviewer also suggested that we should remove planarians and plant story from this manuscript. However, we think these stories make our manuscript very distinct from previous works made by others. Also, contrary to

reviewer 1, the reviewer 3 highly appreciated these stories. Accordingly, we decided not to remove these stories from the revised manuscript.

Reviewer 2

This review described the whole aspects of RB. The manuscript was well-organized and informative. The concept was interesting that stem cells and cancer stem cells share characteristics related with RB. Although not many literatures report on RB in iPS cells, it would make this review more attractive to discuss RB and iPS cells because this review was invited from World Journal of "Stem Cells". Were there any speculations about RB in maintenance of pluripotency or self-renewal? Another point was that tissue specific stem cells and RB. Were there any literatures on tissue specific transcription factors and RB?

→We are again very much delighted to see this reviewer's high evaluation. This reviewer suggested that we should discuss on the relationship between RB and iPS cells. We are afraid that this reviewer might have missed, but we already discussed on it in the original version of manuscript. However, to more strengthen the discussion, we inserted new sentences into the section of 'iPS/ES cells' that was described from the aspect of the point suggested by this reviewer.

→ We also discussed on the role of tissue specific transcription factors in RB-mediated control of stem cell activity. However, to more strengthen the discussion, we inserted new sentences into the section of 'tissue specific transcription factors' from the aspect of the point suggested by this reviewer.

Reviewer 3

The manuscript by Kohno et al. "RB tumor suppressor functions shared by stem cell and cancer cell strategies" summarizes the impact of retinoblastoma 1 on the maintenance of stem cells and the direction of their differentiation. The authors compare RB1 function to its role in induced pluripotency, transformation, and cancer cells. Kohno et al. cite a wealth of publications to

stress the concept that besides the well-known function RB1 in repression of the cell cycle the protein is also involved in regulation of plasticity and chromosomal stability. They describe examples from plants to mammalian embryonic stem cells and diverse cancer types. The review is up to date but often description and suggested concepts could be more precise throughout the manuscript. An example is the first sentence of the abstract.

→We are again very much delighted to see this reviewer's high evaluation. This reviewer suggested some of concepts could be more precise throughout the manuscript. To strengthen our manuscript from the aspect that this reviewer pointed out, we inserted new sentences into the new version of manuscript. Additionally, we improved the first sentence of the abstract where this reviewer indicated that it should be improved.

We also polished English again.

We are looking forward to having positive response soon.

Sincerely,

Dec. 17, 2015

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