Peer Review File

Article information: https://dx.doi.org/10.21037/aob-21-3

Reviewer comments

Reviewer A

Comment 1: First of all, there is no doubt that CTLA4 and PD1 are the most known immune checkpoint targets but many other signaling pathways have been studied recently, some of them with very promising results. Without mentioning new targets, this manuscript will be very repetitive and lacks innovation.

The TNF-TNFR2 signaling pathway is one of those. It has been clearly shown that Blocking this signaling pathway can interrupt the immunosuppression by T cells and many others. Please refer to the following articles to build up this section. PMID: 33344453, PMID: 32669116, PMID: 32546175, PMID: 33303019, PMID: 32698887, PMID: 33397378, PMID: 27506541 and PMID: 33391276.

Reply 1: As advised, we refer to the above literature and some other literature to build the section '3.6. Tumour necrosis factor receptor 2 (TNFR2)'.

Changes in the text: See Page 19-21, line 403-446.

Comment 2: Second of all, AOB is a blood-related journal. This manuscript discusses solid tumors and not liquid ones.

Reply 2: As advised, we discuss hematological neoplasia about CTLA-4 and PD-1 signaling pathways and the applications in clinical situations.

Changes in the text: See Page 8-9, line 176-182; Page 12, line 244-249 and Page 12-13, line 260-266.

Comment 3: The English level needs to be improved.

Reply 3: When the manuscript was initially completed, we had invited a professional language editing service agency(https://asiaedit.com/) to modify our review. The relevant editing certificate is in the attachments. In this round of responses to reviewers, we asked our native English-speaking colleagues to make corrections in english writing such as grammar and tense.

Comment 4: Please add some references on pages 3 and 4, lines 55 to 88. This comment is correct in many other sections. Please after each piece of fact give a reference.

Reply 4: We added some references:

1) Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013;342:1432-1433.

2) Starr TK, Jameson SC, Hogquist KA. Positive and negative selection of T cells. Annu Rev Immunol 2003;21:139-176. And a website: https://www.nobelprize.org/prizes/medicine/2018/press-release/.

Changes in the text: See Page 3-4, line 55-85.

Comment 5: This manuscript strongly lacks some descriptive figures. The authors have to prepare some figures at least for CTLA4 and PD1 pathways.
Reply 5: We added 2 figures for CTLA4 and PD1 signaling pathways respectively.
Changes in the text: See Fig.1 for CTLA4 signaling pathway and Fig.2 for PD1 signaling pathway.

Comment 6: In the CTLA4 and PD1 sections, the authors have to elaborate more about Tregs.
Reply 6: As advised, we elaborate about Tregs in the CTLA4 and PD1 sections.
Changes in the text: See Page 7, line 142-149 and Page 11, line 225-230.

Reviewer B
Comment 1: This review is well written and provides valuable information, but in the form, I have received in pdf file there are no tables of figures. The review would benefit from figures and tables showing the mechanisms and also the applications in clinical situations.
Reply 1: We added 2 figures for CTLA4 and PD1 signaling pathways respectively.
Changes in the text: See Fig.1 for CTLA4 signaling pathway and Fig.2 for PD1 signaling pathway.

Comment 2: Of note, there are also other markers of the immune checkpoint that could be described.
Reply 2: As advised, we add other 4 immune checkpoint: TNFR2, 4-1BB, CD27 and ICOS.
Changes in the text: See Page 19-24, line 403-512.

Comment 3: The authors could also describe the immune checkpoint therapy in solid cancer but as well as in hematological neoplasia (which behaves differently).
Reply 3: As advised, we discuss hematological neoplasia about CTLA-4 and PD-1 signaling pathways and the applications in clinical situations.
Changes in the text: See Page 8-9, line 176-182; Page 12, line 244-249 and Page 12-13, line 260-266.

Comment 4: The authors should also highlight more that some of the immune checkpoint's mechanisms are inhibitory while other molecules are activators, and depending on the situation the effect is different for the same molecule.
Reply 4: As advised, we add some costimulatory molecules, with a conclusion of inhibitory and costimulatory molecules, and bidirectional functions of the same molecule.
Changes in the text: See Page 5, line 100-103 and Page 21-24, line 447-512.