Reviewer's report

Title: Over-expressing Akt in T cells to resist tumor immunosuppression and increase anti-tumor activity

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Reviewer: Yukai He

Reviewer's report:

One of the main obstacles to the success of immunotherapy is the effector phase failure of immune effector cells at tumor microenvironment. In this study, the authors studied to engineer the T cells and equip them with resistance to tumor induced immune suppression. This is a very interesting work and worth careful examination. The study is straightforward and the dataset is supportive. It should generate broad interest in the field of immunotherapy and may open a new field for manipulating immune effector to achieve more effective antitumor effect in the setting of adoptive T cell transfer.

However, one recent report (Crompton et al, Cancer Research 2015) demonstrated that Akt inhibition during T cell activation could enhance generation of memory cells, which result in improved antitumor effect upon adoptive transfer. In revision, the authors need to comment on this paper.

In addition, there are several minor issues that can be addressed to increase the quality of this paper.

1. It will be very helpful for readers to grasp the main points if subtitles are used in the text of the “Result Section”. For example:

a. The first main point (Fig.1) can be subtitled: Akt expression in the T cells is down-regulated in the tumor microenvironment.

b. Secondly, the data in figures 2-3 are collectively to support the main point that ectopic expression of Akt in OT-1 cells enhance antitumor effect in mouse B16 melanoma model

c. Figure 4-6 are trying to demonstrate that human T cells engineered to express Akt also equip them with better antitumor function.

2. What percent of human T cells are actually transduced with retrovirus to express EpCAM CAR? Can it be examined by immunohistochemical staining? If not, EGFP-expressing retrovirus may be used to indirectly show the percentage of transduction. By doing so it will reveal how effective of the CAR-T in treating human prostate cancer in mice.

3. For Figure 4, it is necessary to present a summary graph showing the average and mean of a number of samples and statistical analysis. In other word, readers will know the data is not just from one sample and one experiment.
**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I have no competing interest