

## Reviewer Report

**Title: A MAP of tumor-host interactions in glioma at single cell resolution**

**Version: Original Submission**    **Date: 5/4/2020**

**Reviewer name: Valentine Svensson**

### Reviewer Comments to Author:

#### # Review

In this paper the authors use a large collection of scRNA-seq glioma data to identify cells from hosts which communicate with tumor cells. They identify a large number of interesting interactions specific to subtypes of tumors and various non-neoplastic cells. These interactions would be of great value to the scientific and medical community. It is however not clear how much trust should be put in the identified interactions. The authors greatest tool available to prove this trust is the large number of patients, which is under-utilized for statistical analysis.

The authors make use of a number of rank-based statistics methodology, and in particular use imputed gene expression which is highly likely to produce over-confident expression levels and a large number of false positives.

#### # Major issues

- The most convincing results are those which are replicated between many individual patients. The authors need to quantify these results with some statistical analysis. It appears substantial that an interaction is preserved across e.g. 20 out of 39 patients, or 11 out of 30 patients. But how much more is that than would be expected by chance? The authors can use some form of binomial test to quantify this, with some randomization strategy to identify what the probability of success for the null hypothesis should be.

- Similar to this point, can a similar quantification be made regarding identifying the validated L-R interactions from the Govek et al paper? Is it significant that 3 interactions are present among the top 10 identified interactions?

#### # Minor issues

- It is not clear what 'relevant cells' refer to on page 9. Is it how large the fraction of a cell type is? Or how many potential communication partners they appear to have?

- The argument for why the custom developed scTHI score would not suffer from the same issues as the mean expression based scores in previous publications is unclear.

- The authors claim that the use of ranked expression values is more stable than observed counts to compare gene pairs, yet provide no citation nor demonstration.

- In the discussion section, when writing cell types are 'associated', do the authors mean they have the ability to communicate?

## Methods

Are the methods appropriate to the aims of the study, are they well described, and are necessary controls included? Choose an item.

### **Conclusions**

Are the conclusions adequately supported by the data shown? Choose an item.

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