

## Point by point responses to reviewers

Dear editor Ma:

Thank you for your hard work and your email in which you encouraged us to review our manuscript. The comments from the reviewers are positive and constructive, and are very important to the improvement of our manuscript. We have revised our manuscript, point by point, according to the comments and suggestions, and submit the revised version to you.

Best wishes,

Haiwen Lu

Responses to reviewers' comments:

**Reviewer 1:** The study showed the inhibitory effects of astragaloside IV on cancer-associated fibroblasts via regulation of miRNAs, and several molecules of oncogenic or tumor suppressive factors. From the results, the authors insisted that astragaloside IV may be a potent therapeutic agent regulating tumor microenvironment.

Major comment: #1. The study showed that the changes of miR-214, 301a, M-CSF, TIMP, SOX2, NANOG in GCAF and BGC-823 cells according to the treatment of astragaloside IV. However, direct interactions was not shown among these molecules. So, we could not clearly conclude that some of molecular changes are just bystander effects. For more in depth investigation or discussion seems to be necessary for the action mechanism of astragaloside IV on these selected molecules.

**Response:** This is a constructive comment valuable for the improvement of our manuscript. We have supplemented four paragraphs in the "Discussion" section to interpret the interactions among the molecules and elucidate the internal relationships among their expression changes. These contents will provide readers with a more clear and deeper understand about the manuscript. The supplemented paragraphs are marked using the "Track Changes function" of Microsoft word in the revised version.

Recently, we have started to investigate more compounds in other herbs. In the new investigations, we will pay more attention on studying and exploring the direct interactions between different target molecules. When we prepare our new articles, we will cite this paper in time.

**Reviewer 2:** The study comprises in vitro results only but these are important results for astragaloside IV. Work on cancer-associated fibroblasts is very important and I congratulate the authors for their work.

Classification: Grade B (Very good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Accept

**Response:** We sent the manuscript to an English language editing company, and the language has been polished by a native speaker from America.