SAMSUNG MEDICAL CENTER
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April 19, 2024

# Response to Reviewer 2 Comments

Dear Editor of International Journal of Molecular Sciences

I am writing to submit a revised version of our manuscript entitled **"Migratory tumor cells cooperate with cancer associated fibroblasts in hormone receptor-positive and HER2-negative breast cancer"** for consideration for publication in IJMS.

We are very grateful for the detailed review of our manuscript, as it will greatly enhance the quality of our paper. In response to the reviewer's comments, we have made major revisions to the manuscript. The changes have been highlighted in re-submitted manuscript file. Additionally, we have provided the table below detailing the revisions made, addressing each point raised by the reviewer.

| No. | Comments | Response | Rows |
|---|---|---|---|
| (1) | Introduction lacks paragraph related to objectives. | Thank you for your valuable feedback. I appreciate your suggestion to enhance the introduction for our goals. I additionally incorporate this aspect to better align the introduction with the overall aims of the study.<br>**Revised manuscripts:**<br>In this study, we aimed to demonstrate the efficient integration analysis of two complementary single-cell methods. Droplet scRNA-seq was used to evaluate the heterogeneity of tumors and their microenvironmental cells from a large population of cells, and SIDR-seq is for the linkage between transcriptomic characteristics and genetic alterations.<br>Our primary objective was to identify distinct tumor cell type that plays a significant role in the behavior or dynamics of this type of breast cancer, when considering both transcriptomic and genetic features. Additionally, we aimed to elucidate the collaborative interactions of these cell type with the tumor microenvironment. | Rows 61 - 70 |

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| (2) | Rows 53-64 are more like a conclusion and probably would fit better in that section | Thank you for your suggestion. You're right that the content from rows 53-64 reads more like a conclusion. We moved this content to the conclusion section for better organization. | Rows 365 - 370 |
| (3) | The number of patients was extremely low considering that it is a common breast cancer subtype | Thank you for bringing this to our attention. We recognize and deeply consider the limitation posed by our small sample size, viewing it as a matter of utmost importance issue of our study. The limited sample size is partly due to the need to select tumor masses with relatively larger sizes, as various library construction methods were applied to generate our data. Additionally, our budget constraints significantly restricted for sequencing. The sequencing processes are quite expensive, and we managed to conduct our research within these financial limitations. Unfortunately, this limitation resulted in a smaller sample size than we initially desired, despite the HR+/HER2- breast cancer is very common type. Larger studies with more patients are indeed necessary to validate and further explore the implications of our results. | - |
| (4) | The Results section precedes the Materials and Methods section (this is wrong) | Thank you for pointing out the order of the sections. We appreciate your feedback and apologize for any confusion it may have caused. Initially we used manuscript template provided by IJMS. We will address this issue with the editors of IJMS and make the necessary adjustments to ensure the correct order of sections in our manuscript. | - |

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| (5) | Please add trial limitations and, also add Conclusions section | We have added a Conclusion section to summarize the key findings and implications of our research. Additionally, we clearly explained the trial limitations of our study. I'm very grateful that our paper was better organized thanks to your suggestions.<br>**Revised manuscripts:**<br>The limitation of this study is inability to directly establish migratory tumor prognosis due to small sample size and short follow-up. Additionally, distinct tumor properties, including migration and stemness, were not definitively confirmed experimentally. Thus, larger studies and advanced techniques are needed to fully understand the role of migratory phenotype tumor cells in HR+/HER2- BC and their interactions with TME cells. | Rows 365 - 382 |

Thank you for your consideration of our revised manuscript. We believe that the changes we made have significantly improved the quality of the manuscript, and we look forward to your feedback.

Sincerely,

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