

### **Review Comments**

The manuscript contains significant discrepancies that need to be addressed.

1. The title states, "Postexercise downregulation of NUP155", which contradicts the findings.

Reply: First and foremost, we sincerely apologize for any confusion caused by the title "Postexercise downregulation of NUP155." We greatly appreciate your pointing out this issue and providing us with the opportunity to clarify.

The central findings of our study are that, in the GSE41914 dataset, the expression of the NUP155 gene is significantly lower in samples after exercise compared to before exercise (as shown in Figure 1A and 1D). In contrast, in the TCGA-NSCLC dataset, the expression of the NUP155 gene is significantly higher in non-small cell lung cancer (NSCLC) samples than in normal samples (as shown in Figure 1B and 1E). Further in vitro experiments confirmed the upregulation of NUP155 in NSCLC and showed that knocking down NUP155 could inhibit the proliferation, migration, and invasion of lung cancer cells, while promoting apoptosis. Additionally, we found that knocking down NUP155 could inhibit cell invasion and migration through the PTEN/AKT signaling pathway.

NUP155 is downregulated after exercise, and downregulating NUP155 in NSCLC can inhibit cell proliferation. Based on these findings, we hypothesize that the downregulation of NUP155 after exercise may help inhibit the occurrence and development of NSCLC. Therefore, our research title "Postexercise downregulation of NUP155 in regulating non-small cell lung cancer progression via the PTEN/AKT signaling pathway" accurately reflects our research results and conclusions.

Upon your valuable feedback, we conducted a thorough review of the entire manuscript and identified incorrect descriptions of the results. We deeply regret this and have immediately corrected these errors to ensure that the article accurately reflects our research findings. We are grateful for your meticulous review and valuable comments and pledge to continue striving to ensure that our research work meets the highest standards of quality and accuracy.

Changes in the text: In the lines 43-44, 278 and 358-359.

2. In the Results section, Figure 1D clearly shows that NUP155 expression levels were higher in postexercise samples compared to pre-exercise samples in the GSE41914 dataset.

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Reply: We would like to express our sincere apologies for the confusion caused by our unclear description in the Results section regarding Figure 1D. We appreciate the opportunity to clarify this matter. Firstly, as shown in Figure 1A, a total of 589 upregulated and 299 downregulated differentially expressed genes (DEGs) were identified between pre-exercise and post-exercise samples in the GSE41914 dataset, with NUP155 being significantly downregulated. Secondly, Figure 1D demonstrates that the expression levels of NUP155 are significantly lower in post-exercise samples compared to pre-exercise samples within the GSE41914 dataset. We deeply apologize the error in our description that led to this confusion. We have made the necessary corrections to the manuscript to accurately reflect our findings. We are grateful for your patient guidance and for providing us with the opportunity to address this issue.

Changes in the text: In the lines 43-44, 278 and 358-359.

3. The abstract states: "NUP155 was significantly upregulated in NSCLC and postexercise samples", which aligns with the results but contradicts the title.

Reply: Thank you for bringing to our attention the discrepancy between the abstract and the title of our manuscript. We appreciate your vigilance and the opportunity to correct this inconsistency. Upon your feedback, we have promptly revised the abstract to accurately reflect the findings of our study. The incorrect statement "NUP155 was significantly upregulated in NSCLC and postexercise samples" has been replaced with "NUP155 was downregulated in postexercise samples and upregulated in NSCLC samples, indicating its association with poor prognosis in NSCLC." With this amendment, the abstract now aligns with the title and accurately represents the results of our research. We are grateful for your meticulous review and for helping us enhance the clarity and accuracy of our manuscript. We believe that with this correction, the article's narrative will be more precise and consistent. Thank you once again for your attention to detail and for your valuable input.

Changes in the text: In the lines 43-44.

4. The study did not directly measure post-exercise NUP155 levels in NSCLC cell lines; cell line experiments were used to investigate the functional role of NUP155 in NSCLC rather than to study post-exercise effects directly.

Reply: Thank you for your observation regarding the study's limitations in directly measuring post-exercise NUP155 levels in NSCLC cell lines. We acknowledge this as a limitation in our current research and appreciate your feedback. In our study, we utilized bioinformatics to assess the expression levels of NUP155 before and after exercise, as well as to analyze the expression levels of NUP155 in non-small cell lung cancer (NSCLC) samples compared to normal samples. Subsequently, we conducted in

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in vitro experiments to investigate the functional role of NUP155 in NSCLC, rather than directly studying post-exercise effects. We recognize that not directly measuring NUP155 levels in NSCLC cell lines after exercise is a limitation, which is due to the current limitations of experimental conditions. To address this, we plan to undertake the following in our future research: Directly measure post-exercise NUP155 levels in NSCLC cell lines to understand the acute effects of exercise on NUP155 expression. This will provide a more direct link between exercise and NUP155 expression dynamics in NSCLC cells. Investigate the impact of exercise on NUP155 expression in preclinical models, such as xenograft models. This approach will help bridge the gap between in vitro cell line studies and the in vivo situation, offering a more comprehensive understanding of how exercise might influence NUP155 expression and function in a physiological context. We are committed to addressing this limitation and expanding our research to provide a more comprehensive understanding of the role of NUP155 in NSCLC and the potential for exercise to influence its expression and function. Thank you again for your insightful comments and for giving us the opportunity to clarify and improve our research direction.

Changes in the text: In the line 421-436.

The authors are suggested to eliminate this inconsistency which represents a major flaw in the manuscript. Below mentioned are a few recommendations in this regard;

1. Correct the title to reflect the actual findings (upregulation rather than downregulation).

Reply: Upon your valuable feedback, we conducted a thorough review of the entire manuscript and identified incorrect descriptions of the results. We regret to say that there was an oversight in our description where we stated that "NUP155 expression levels were noticeably higher in postexercise samples than in pre-exercise samples." This was an error on our part, and we sincerely apologize for this mistake. We have promptly corrected this to accurately reflect our findings: "NUP155 expression levels were noticeably lower in postexercise samples than in pre-exercise samples." Our data indicate that NUP155 is downregulated after exercise, and this downregulation can inhibit cell proliferation in NSCLC. Based on these findings, we hypothesize that the postexercise downregulation of NUP155 may contribute to the inhibition of NSCLC occurrence and progression. Consequently, our research title "Postexercise downregulation of NUP155 in regulating non-small cell lung cancer progression via the PTEN/AKT signaling pathway" accurately captures our research results and conclusions. We deeply apologize for the confusion caused by our writing error that

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led to a contradiction between the study results and the title. We are grateful for your guidance and valuable comments on our manuscript.

Changes in the text: In the lines 43-44, 278 and 358-359.

2. Review and revise all statements throughout the manuscript to ensure consistency with the observed upregulation of NUP155 after exercise.

Reply: Thank you for your directive to ensure consistency in the representation of NUP155 expression levels throughout the manuscript. We have conducted a comprehensive review of the entire document, and we have made the necessary revisions to align all statements with our observed findings. We have corrected all instances where the expression of NUP155 was incorrectly represented. Now, the manuscript accurately reflects that NUP155 expression levels are lower in post-exercise samples compared to pre-exercise samples, and higher in non-small cell lung cancer (NSCLC) samples compared to normal samples. We have also ensured that these corrections are consistent with the figures and results presented in the study, maintaining the integrity and accuracy of our scientific findings. We appreciate your guidance in helping us maintain the highest standards of scientific rigor and clarity in our work.

Changes in the text: In the lines 43-44, 278 and 358-359.

3. Discuss the implications of NUP155 upregulation after exercise in the context of NSCLC progression.

Reply: We are grateful for your insightful comments and guidance. The downregulation of NUP155 after exercise in the context of NSCLC progression suggests several potential implications. Firstly, as NUP155 is upregulated in NSCLC and its knockdown inhibits cell proliferation, migration, and invasion, promoting apoptosis, the exercise-induced reduction in NUP155 could be interpreted as a beneficial response that counteracts the aggressive behavior of NSCLC cells. This downregulation may contribute to the suppression of tumor growth and metastasis, which are key hallmarks of cancer progression. Moreover, the modulation of NUP155 through exercise could impact the PTEN/AKT signaling pathway, which is crucial in regulating cell survival and metabolism. By inhibiting cell invasion and migration through this pathway, the downregulation of NUP155 post-exercise may provide a mechanism by which physical activity can influence cancer outcomes. In summary, the downregulation of NUP155 following exercise may offer a multifaceted approach to inhibit NSCLC progress by directly targeting cancer cell proliferation and invasion. These findings underscore the need for further research to fully elucidate the mechanistic links between exercise,

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NUP155 expression, and NSCLC progression. Thank you once again for your valuable feedback, and we appreciate your contribution to the quality of our research.

Changes in the text: In the lines 401-420.

4. Clearly explain the limitations of using NK cell data to infer exercise effects on NSCLC cells.

Reply: Thank you for your question about the limitations of extrapolating the effects of exercise on NSCLC cells from NK cell data. It's important to clarify that NK cell responses to exercise do not fully represent the direct effects on NSCLC due to the distinct cellular mechanisms, the complexity of the tumor microenvironment, and the lack of direct cellular response data. The interaction between NK cells and NSCLC cells is complex, and changes in NK cell function may not be a direct measure of how NSCLC cells respond to exercise. We acknowledge these limitations and appreciate your feedback as we continue to explore the relationship between exercise, immune responses, and NSCLC progression. We appreciate your attention to this important aspect of our study and will consider these limitations in our future research endeavors.

Changes in the text: In the lines 421-436.