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Response to Letter to the Editor: Potential of SPHK1 as a prognostic marker and therapeutic target in colorectal cancer: insights from bioinformatics and experimental analysis

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Dear Editor,

We are truly grateful to Du *et al*[1] for their insightful Letter to the Editor, offering a comprehensive commentary on our recent publication, "Potential of SPHK1 as a prognostic marker and therapeutic target in colorectal cancer: insights from bioinformatics and experimental analysis"[2]. Their positive appraisal of our multi-omics integration and experimental validation significantly reinforces the burgeoning understanding of sphingosine kinase 1 (SPHK1) in colorectal cancer (CRC) progression. We particularly appreciate their emphasis on SPHK1's crucial roles in epithelial–mesenchymal transition and immune infiltration, which aligns seamlessly with our initial findings and further highlights the multifaceted impact of this enzyme. Engaging with such thoughtful critiques is vital for advancing scientific discourse and refining research methodologies. To ensure the transparency and rigor of our idea, this study adheres to the TITAN 2025 Guideline Checklist[3]. The detailed information of TITAN Guidelines 2025 is indicated in Supplemental Digital Content Table S1, available at: http://links.lww.com/JS9/G568.

Du *et al* astutely identified three pivotal limitations within our study: (1) the absence of *in vivo* animal experiments, (2) limited sample sizes in specific validation cohorts, and (3) an incomplete elucidation of SPHK1's upstream regulatory network. We welcome this opportunity to directly address these points, providing context for our original research scope and outlining our proactive, ongoing efforts to strengthen the evidence base and propel our findings toward clinical translation (Supplemental Digital Content Table S2, available at: http://links.lww.com/JS9/G569).

First, regarding the critical need for *in vivo* validation, our initial investigation primarily focused on robust bioinformatics analyses and targeted *in vitro* experimental models to identify SPHK1 as a promising candidate. While this approach effectively established a strong correlative and mechanistic foundation, we wholeheartedly concur with Du *et al* that definitive animal model data are indispensable for translating preclinical findings into clinical relevance. To bridge this gap, our research group has since embarked on a comprehensive follow-up study specifically designed for *in vivo* validation. We are actively establishing various animal models, including subcutaneous and orthotopic xenografts in immunodeficient mice, and exploring patient-derived xenograft models. These models will allow us to rigorously assess whether SPHK1 modulation (e.g., through genetic knockdown via shRNA/CRISPR or inhibition with small molecules) impacts primary tumor growth, metastatic potential, and overall survival within a complex physiological environment. The comprehensive results from these rigorous ongoing experiments will be meticulously analyzed and presented in a forthcoming manuscript, underscoring our commitment to a holistic understanding of SPHK1's role.

Secondly, concerning the perceived limitations in cohort sample sizes for certain analyses, our original meta-analysis synthesized data from numerous public datasets, encompassing over 1200 patients (e.g., TCGA, GSE39582[4], and GSE87211[5]). This extensive pooling provided high statistical power for overall prognostic associations (e.g., HR > 1 across cohorts, $P < 0.05$). However, we acknowledge that specific data types, such as DNA methylation profiles, were only available in smaller, more specialized cohorts (e.g., $n = 36$ for GSE103479[6]). To mitigate potential biases and enhance the generalizability of our findings, we performed rigorous sensitivity analyses, which consistently upheld SPHK1 as a robust high-risk factor. Furthermore, recognizing the importance of diverse and larger patient cohorts, we have initiated collaborative efforts to establish a multi-center prospective cohort. This initiative involves collecting samples from hundreds of additional CRC patients with detailed clinical

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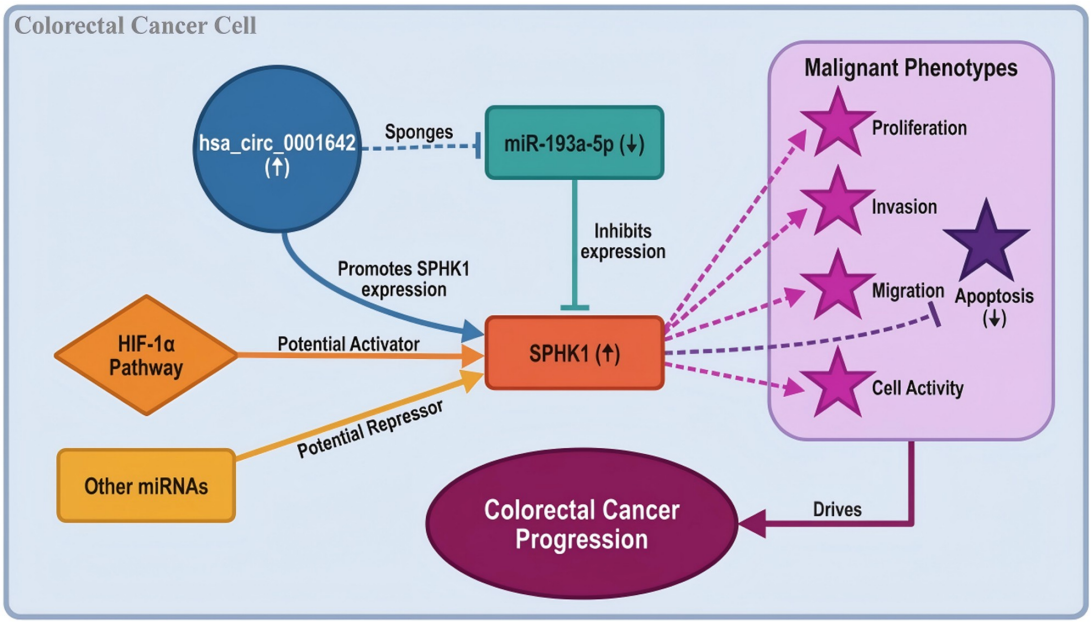

Figure 1. Schematic diagram of the molecular mechanism underlying hsa_circ_0001642-mediated colorectal cancer progression. The schematic illustrates the proposed regulatory axis within a colorectal cancer cell. Upregulated hsa_circ_0001642 functions as a molecular sponge for miR-193a-5p, thereby relieving the suppressive effect of miR-193a-5p on its target gene, sphingosine kinase 1 (SPHK1). Consequently, increased SPHK1 expression promotes malignant cellular phenotypes, including enhanced proliferation, invasion, migration, and cell activity, while inhibiting apoptosis. Additionally, the HIF-1α pathway acts as a potential activator, while other miRNAs serve as potential repressors of SPHK1. Collectively, this axis drives the overall progression of colorectal cancer. The solid arrows indicate promotion or activation, while the T-bars indicate inhibition.

follow-up data, enabling us to validate our bioinformatics predictions with even greater statistical robustness and clinical applicability.

Thirdly, addressing the incomplete elucidation of SPHK1's upstream regulatory network, we agree that understanding the molecular mechanisms driving SPHK1 dysregulation is paramount for developing targeted therapeutic strategies. Our original study identified correlative methylation patterns. Building upon this, our in-depth investigations into SPHK1's regulatory landscape have yielded exciting new findings, particularly concerning non-coding RNAs. We have recently identified a novel circular RNA, hsa_circ_0001642, which significantly promotes CRC malignant behaviors. *In vitro* assays consistently demonstrated that knockdown of hsa_circ_0001642 markedly mitigated these phenotypes, including reduced cellular proliferation, significant declines in invasion and migration capabilities, diminished cellular activity, and elevated apoptosis rates. Mechanistically, we elucidated that hsa_circ_0001642 orchestrates this malignancy by directly modulating SPHK1 expression, acting as a molecular sponge for miR-193a-5p (Fig. 1). This detailed regulatory axis, linking a novel circRNA to SPHK1 via a specific miRNA, provides a concrete example of the complex upstream regulation we are actively unraveling. This comprehensive work is currently being prepared for publication. Furthermore, drawing upon existing literature[7,8] and advanced bioinformatics screening, we are also actively investigating other potential regulators such as the hypoxia-inducible factor 1-alpha (HIF-1α) pathway and additional miRNAs that may exert post-transcriptional control over SPHK1. The ultimate goal of these studies is to unravel the intricate signaling pathways that converge on SPHK1, potentially revealing novel druggable targets for CRC intervention.

In conclusion, Du *et al*'s perceptive commentary has not only affirmed the potential of SPHK1 as a critical biomarker and therapeutic target in CRC but has also provided invaluable guidance for refining our ongoing research trajectory. Their insights motivate our continued commitment to robust experimental validation and mechanistic elucidation. We are confident that our current *in vivo* and molecular investigations will substantially contribute to the growing body of knowledge on SPHK1, ultimately paving the way for more effective, SPHK1-targeted therapeutic strategies for patients battling CRC. We look forward to continued dialogue and collaboration in advancing precision oncology.

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Author contributions

Y. -J. N.: Formal analysis, Resources, Methodology, Software, Visualization, Writing – original draft. H. -P. Z.: Formal analysis,

Resources, Methodology, Software, Visualization, Writing – original draft. Y.-D.M.: Conceptualization, Funding acquisition, Project administration, Writing – review & editing. All authors reviewed the manuscript.

Conflicts of interest disclosure

The author declares no conflict of interest.

Declaration of whether any AI was used in the research and manuscript development

In accordance with the TITAN 2025 Guideline Checklist (https://premierscience.com/pjs-25-950/), we declare that generative AI tools (Gemini 3 Pro) were solely used for language polishing, including grammatical correction and sentence structure refinement. All scientific content, data interpretation, and conclusions remain the sole responsibility of the authors, with no AI involvement in substantive revisions.

Data availability statement

The data included in the study are available from the corresponding author upon reasonable request.

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