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Peer Review

Review of: "Kinase Suppressor of Ras 2 Promotes Self-Renewal and Clonogenicity of Small-Cell Lung Carcinoma"

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Review of Manuscript Entitled: Kinase Suppressor of Ras 2 Promotes Self-Renewal and Clonogenicity of Small-Cell Lung Carcinoma

Summary : In this manuscript, the authors provide an in-depth analysis of the role of Kinase Suppressor of Ras 2 (KSR2) in facilitating self-renewal and clonogenicity in small-cell lung carcinoma (SCLC), particularly focusing on the SCLC-A subtype. The authors meticulously detail the experimental protocols employed throughout their studies, ensuring that the methodology is transparent and reproducible.

The manuscript presents a substantial body of research, comprising both in vitro and in vivo experiments conducted with a high degree of scientific rigor. Key components of the study include the establishment and characterization of knockout cell lines targeting KSR2, which allows for a direct assessment of its functional significance in cancer biology. Additionally, the authors performed immunoprecipitation assays to elucidate the interaction partners of KSR2, further advancing our understanding of its molecular mechanisms.

Furthermore, the expression levels of KSR2 transcripts were quantified in normal tissue samples as well as in various mouse tumor models, offering insights into the differential regulation of this kinase in cancerous versus healthy environments. The investigation also assessed SCLC clonogenicity through colony formation assays and evaluated cell viability using appropriate cytotoxicity assays.

Overall, the extensive research presented in this manuscript contributes valuable knowledge to the field of small-cell lung carcinoma, highlighting the potential of KSR2 as a therapeutic target. Given

 doi.org/10.32388/93B9Y6

the thoroughness and significance of the findings, this work is well-deserving of publication.

Minor Comments:

1. Is a relevant reference missing, or are the authors relying on ACS data? The five-year relative survival rates for patients with small cell lung cancer (SCLC) with localized, regional, and distant disease are 30%, 18%, and 3%, respectively (American Cancer Society, 2024).
2. Figure 2A can be moved to the supplementary information, as the FACS plots do not provide significant insights.
3. The data presented in Fig 2B lacks a detailed explanation, making it difficult to interpret the significance of the results. It is noted only that Kp1 was treated with short hairpin RNAs (shRNAs), but there is no further context regarding the outcomes measured. Additional information on the implications of the findings would greatly enhance the understanding of the presented data.
4. The authors have not explored the scaffold aspect of KSR2. The authors have not thoroughly investigated the scaffold function of KSR2, which plays a critical role in signaling pathways and cellular processes. This oversight limits our understanding of how KSR2 might interact with other proteins and contribute to cellular signaling dynamics. A detailed exploration of KSR2's scaffold properties could reveal its potential implications in various biological functions and disease mechanisms.
5. The conclusions drawn are truly enlightening and significantly enhance the ongoing dialogue. However, the KSR2-ERK narrative, while grounded in previous research, has yet to be explored through comprehensive experimental studies.
6. What is the rationale for including the reference to JQ1 in the last paragraph? Specifically, how does it contribute to the overall argument or theme presented in the text, and what implications does it have for the reader's understanding of the subject matter?

Declarations

Potential competing interests: No potential competing interests to declare.