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Peer Review

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

Jonas Wolf[1]

1. Hospital Moinhos de Vento, Porto Alegre, Brazil

This manuscript presents compelling evidence that Kinase Suppressor of Ras 2 (KSR2) functions as a critical regulator of tumor propagating cell (TPC) self-renewal and clonogenicity in the ASCL1 subtype of small-cell lung carcinoma (SCLC-A). The identification of KSR2 as a molecular scaffold promoting Raf/MEK/ERK signaling specifically in this subtype offers a nuanced understanding of the molecular heterogeneity underlying SCLC and contributes valuable insight into potential mechanisms of tumor initiation and maintenance.

One of the study's key strengths lies in its focus on the ASCL1 subtype, which remains understudied despite its clinical relevance and prevalence among SCLC cases. By establishing a subtype-specific role for KSR2, the research advances the field's understanding of molecular vulnerabilities within SCLC subtypes. The demonstration that KSR2 expression is enriched in pulmonary neuroendocrine cells (PNECs)—known cells of origin for SCLC-A—further reinforces the biological plausibility of the proposed model and suggests an ontological link between normal progenitor states and tumorigenic transformation.

The functional assays provide robust evidence for the requirement of KSR2 in TPC self-renewal and tumor initiation. The use of both in vitro colony formation assays and in vivo tumor initiation experiments represents a methodologically strong approach that convincingly supports the central hypothesis. Particularly noteworthy is the emphasis on the interaction between KSR2 and ERK, suggesting that KSR2 exerts its effects through a well-defined signaling cascade. This mechanistic anchoring provides a clear framework for future research into targeted interventions.

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An important conceptual contribution of this work is the repositioning of KSR2 from its traditionally understood role in metabolism and MAPK signaling to one directly involved in cancer stem-like behavior. This shift in understanding opens up new avenues of investigation regarding the dual role of scaffold proteins in both normal cellular signaling and malignant progression. Furthermore, identifying KSR2 as a novel biomarker for SCLC-A adds translational potential to the study, which may eventually inform stratified therapeutic strategies.

However, several opportunities for improvement and clarification remain. The study could benefit from a deeper exploration of the downstream transcriptional consequences of KSR2-mediated ERK signaling in SCLC-A cells. Transcriptomic analyses such as RNA-seq following KSR2 knockdown could illuminate gene networks that mediate TPC properties and help define a KSR2-regulated signature that correlates with clinical outcomes or therapeutic resistance.

Another potential enhancement would be the inclusion of data on the expression and function of KSR2 in other SCLC subtypes, such as NEUROD1-, YAP1-, or POU2F3-driven tumors. Although the study clearly focuses on the ASCL1 subtype, a comparative analysis would contextualize the specificity and therapeutic value of targeting KSR2 and help determine whether its role is truly restricted to SCLC-A or extends more broadly across SCLC molecular subtypes.

In terms of mechanistic depth, the manuscript briefly mentions the dependency on KSR2-ERK interaction but lacks sufficient molecular detail regarding how this interaction influences downstream chromatin remodeling or metabolic reprogramming, both of which are relevant to stem-like features in cancer cells. Future work could probe whether KSR2 affects histone modifications, transcription factor activity, or cellular energetics in ways that contribute to TPC maintenance.

The in vivo experiments, while compelling, would benefit from additional controls and quantification of tumor burden, latency, and histological confirmation to ensure that tumor-initiating capacity is indeed altered by KSR2 depletion and not due to off-target effects or compensatory signaling pathways. Including rescue experiments with ERK-independent KSR2 mutants could further validate the specificity of the observed phenotypes.

Overall, the manuscript is well-structured and written with clarity, providing a logical progression from molecular identification to functional consequence and translational relevance. The findings significantly enhance our understanding of subtype-specific mechanisms in SCLC and propose KSR2 as a promising therapeutic target for SCLC-A. With the addition of broader comparative data, deeper mechanistic exploration, and transcriptomic validation, the impact of this study could be further

amplified. It represents a meaningful step toward unraveling the complexity of SCLC and developing more precise, biology-driven interventions.

Declarations

Potential competing interests: No potential competing interests to declare.