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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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Whereas the read-out of the frequency of tumor propagating cells (colony formation and tumor growth in vivo) is pointing to an intriguing role of KSR2 in SCLC-A cells via its interaction with ERK, the underlying mechanism of how this affects tumor cell propagation remains unclear. The very modest and variable ERK phosphorylation shown in this study primarily serves as a reporter for the scaffold interaction between ERK and KSR2 while apparently being inconsequential for the TPC phenotype. This is in line with previous reports showing that strong Ras signaling is poorly tolerated by SCLC-A cells, although modest signaling has been shown to contribute, e.g., to the metastatic dissemination of SCLC-A. This raises the question of what critical signal is conveyed by this scaffold that includes KSR2 and ERK to promote the self-renewal of these cells. As such, the data rather provide an entrance to follow-up experiments (e.g., through determining the composition of the complex by proteomics and assessing how this affects gene expression). Although the observations are certainly interesting, the work should not stop here but rather serve as a starting point for follow-up work to unravel the signals conveyed by this complex. That might also provide a better inroad into how to intervene in the pathway involved.

The experiments are overall well performed and convincing. Fortunately, the rather modest and somewhat variable ERK phosphorylation appears not too relevant for the conclusions the authors draw, as the experiments using MEK inhibitors and the KSR2r and FIF570r mutants illustrate the prominent importance of the scaffolding role of KSR2 that appears independent from ERK phosphorylation.



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It remains unclear whether the tumors that do grow out upon depletion of KSR2 will finally re-acquire similar TPC capacities as the cells expressing KSR2 (second round of clonal assays) through activating compensatory pathways, which might give insight into what this KSR2 scaffold pathway provides.

Including the different SCLC subtypes is somewhat confusing the message. Next to referring to a role for KSR1 in NeuroD1-positive cells making these cells more susceptible to cisplatin, it would be more interesting to know to what extent there is a role for KSR1 in SCLC-A cells; e.g., is KSR1 required in order to see effects of KSR2?

It would be helpful if the expression of KSR1 and KSR2 is shown in all the cell lines used. As the expression appears to vary quite dramatically (Fig. 1I; what about cell line 2107?), measuring the effects of KSR1 depletion in conjunction with KSR2 might be illuminating. In view of the variable expression of KSR1 and KSR2, it would provide additional comfort if the observed effects are independent of the initial expression levels of these two proteins by showing a slightly larger panel of SCLC-A cells in which this is assessed (e.g., does H711 show the same KSR2 dependence as H1963?).

## Declarations

**Potential competing interests:** No potential competing interests to declare.