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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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Dear Dianna H. Huisman, co-workers, and Robert E. Lewis,

Thanks for the opportunity to read your magnificent findings on KSR2 in SCLC-A cell lines. It is tantalizing that KSR2 knockout causes a significant anti-growth effect, while pharmacological inhibition of MEK (trametinib) and presumably of ERK does not inhibit cell proliferation. Notwithstanding, it is significantly appealing that SCLC-A displays expression of KSR2.

Some tangential remarks: KSR1 and 2 are intimately related to the RAF-MEK-ERK effector RAS signaling pathway (Simanshu, Nissley, and McCormick. Cell 2017), however, little attention has been conferred to the field of KRAS mutant lung cancer. KSR-1 was examined in KRAS mutant lung cancer cell lines as a crucial scaffolding protein for RAF, MEK, and ERK (Kim et al. Mol Cancer Res 2016), where GEH-H1 (encoded by ARHGEF2 expression) dephosphorylates the kinase suppressor of RAS (KSR-1), resulting in its translocation to the plasma membrane and increased MAPK signaling (Cullis et al. Cancer Cell 2014; Kashyap et al. Cell Reports 2019).

The binding of KSR2 to BRAF prompts me to surmise a potential therapeutic effect of v-ATPase inhibitors that have demonstrated potency against cells expressing KRAS/BRAF mutant rather than wild-type genes (for example, in MDA-MB-231 cells, breast adenocarcinoma KRASG13D and BRAFG464V) (Tolani et al. Nature Biotechnology 2022).

It could be of interest whether SCLC-A expressing KSR2, by hyperactivating ERK, enhances UPR proteins such as the inositol requiring enzyme 1alpha (IRE1a) and the potential sensitivity to IRE1a inhibitors such as ORIN1001 (Lv et al. Science 2023).

doi.org/10.32388/1JWYEW

I would be delighted to be in touch if you feel it necessary. All in all, excellent findings of great relevance, with the hopes that you can expedite matters for a prompt publication.

Declarations

Potential competing interests: No potential competing interests to declare.