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Peer Review

Review of: "ARID1A-Induced Transcriptional Reprogramming Rewires Signalling Responses to Drug Treatment in Melanoma"

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ARID1A-Induced Transcriptional Reprogramming Rewires Signalling Responses to Drug Treatment in Melanoma

NB Supplementary figures and tables are not available

The authors interrogate the mechanisms of resistance to MAPK inhibition on a model of melanoma cell line knockout for ARID1A.

The authors perform integrated analysis of transcriptome, proteome, and phosphorylation status of 17 phosphoproteins and kinome activity profiling. The the authors apply matrix factorization and network analysis to identify perturbed pathways and transcription factor regulons on ARID1A KO cells upon MAPK inhibitor treatments.

However description of the results is very chaotic and and is hard to understand. I would suggest to completely restructure the results session by adding all missing information and making easy to understand and follow the flow of the paper.

Before presenting multiomics analysis the authors should provide a description of ARID1A KO cell line.

Figure 1

A.Schematic representation of gene knockout strategy.

B.Western blot or mass spectrometry data demonstrating the lack of protein expression in A375 KO cells

C. IC50 curves for trametinib and vemurafenib to quantify resistance of ARID1A KO cells

 doi.org/10.32388/WCM8VW

D. Description of multiomics integration approach.

In subsequent figures the authors should to describe separately RNAseq, Proteome and phosphoprotein and kinome analysis data with the heatmaps, volcano plots of top differentially expressed genes, proteins and phosphoproteins. In kinome assay section peptide level analysis should be presented. How the peptide phosphorylation data were translated into kinase activity data?

Only after that the authors should present how they integrated above mentioned datasets.

A major criticism goes to the section A**RID1A KO suppresses HLA proteins in both *in vitro* and *in vivo* contexts.**

The authors analyse gene expression alterations in melanoma TCGA dataset by stratifying the patients based on presence of genomic aberrations in *ARID1A*. Again, the description of ARID1A mutations selected for study is missing. Please provide information to make sure that only demonstrated loss-of-function mutations were selected for study. The most important , however, is the fact that it is impossible to assign transcriptional alterations obtained from RNAseq data exclusively to ARID1A mutational status. What is the ARID1A mutated allele frequency in the analysed melanoma tumors? Do these melanomas carry other mutations?

The TCGA data analysis should be carried out carefully with taking in consideration above mentioned factors.

Overall, the authors performed sophisticated computational analysis, however the Materials and Methods section doesn't contain enough information regarding experimental and computational approaches applied.

The same criticism goes to Figure legends. These should be written more carefully by providing detailed description of all provided graphs.(Especially, the legends to Figure1A, Figure 3A and entire Figure 5.)

Declarations

Potential competing interests: No potential competing interests to declare.