Qeios

Peer Review

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

Jochen Imig[1]

1. Chemical Genomics Center of the Max Planck Society, Max Planck Institute of Molecular Physiology, Dortmund, Germany

Review report on “ARID1A-Induced Transcriptional Reprogramming Rewires Signalling Responses to Drug Treatment in Melanoma” by Barker et al., Qeios, 2025

This research investigates the role of ARID1A in conferring resistance to MAPK and BRAF inhibitors in BRAFV600E mutant melanoma cells through multi-omics integration. Genome-wide screens point towards ARID1A's involvement in drug resistance, with ARID1A knockout (KO) cells exhibiting increased resistance to vemurafenib and trametinib. Multi-omics factor analysis (MOFA) revealed distinct adaptive and sustained resistance responses, including novel suppressive players such as PRKD1, and additionally highlighted the rewiring of receptor tyrosine kinase (RTK)-driven signaling. Combination treatments induced phosphorylation patterns linked to DNA damage repair, though they did not significantly alter kinase activity compared to single treatments. Additionally, ARID1A KO was associated with reduced MHC class-II expression, both in vitro and in melanoma patient data, suggesting implications for immune evasion.

The current work holds great novelty and impact for the melanoma community, though it remains largely descriptive and also lacking further experimental validation.

In order to strengthen the impact and robustness of their approach, the authors should consider addressing the following (major) points:

1. The A375 cell line used is commonly employed in melanoma research, but it holds some peculiarities as it appears to be derived from a neural crest stem cell-like origin. The authors may consider transferring some of their key downstream findings to 1-2 other cell lines, e.g., of the

 doi.org/10.32388/H70H2D

highly proliferative and differentiated phenotype (MITF_low), such as a Luminex assay, Kinome analysis, and flow cytometry. Also, it would be interesting to monitor whether an ARID1A knockdown could lead to de-differentiation, indicated by MITF or MelanA expression, which is a typical phenomenon upon targeted therapy resistance and an important characteristic in patient therapy responses.

2. ARID1A is a strong chromatin remodeler. Can the authors data-mine ARID1A knock-down ATAC-Seq and infer the results to their differential RNA-Seq data? That would give strong support to their short-term drug treatment and new exciting ideas about the fast kinetics of opening chromatin conformation and gene expression in melanoma drug resistances.
3. It would be beneficial for the reader to explain the computational frameworks used in a bit more "user-friendly" language for those who are not deeply familiar with computational methods.
4. Both flow cytometric assays for EGFR (Fig. 4c) and HLA-A (Fig. 5c) are missing important negative controls, such as the usage of isotype unspecific antibodies. Quantification (fc or Gmean of fluorescence intensity) of at least n=3 independent replicates is needed to show reproducibility.
5. Supplemental Figures seem to be disclosed. Full review requires access to assess validity and its merit to the field.
6. Kinase assays in A375 for downstream targets of PRKD1 would be greatly beneficial to support the validity of their computational multi-omics analysis. The authors mention such an approach, but the data appear to be missing.
7. The manuscript would greatly benefit from extending their TCGA patient datamining (related to Fig. 5d) to determine whether the cohort of ARID1A negative patients is reflected by an immunological "hot" or "cold" phenotype, i.e., the presence or absence of CD8 or CD4 transcripts indicating a tumor-infiltrating T-cell microenvironment.
8. The authors claim in the last paragraph that: "we reveal that both ARID1A-aected patients and ARID1A KO cells have increased expression of collagens and laminins, which can contribute to increased ECM stiffness, as well as a decrease in HLA proteins (Fig. 5E).". The reviewer is wondering whether such an effect at the transcriptional level in a very short-term treatment is sufficient to be compared with in situ in patients. A discussion addressing this might be helpful.
9. Indication of a raw data repository is needed to show transparency and reproducibility.

Minor:

- One sentence summary: “the study reveals…” it would fit better to phrase that the study describes as some validation experiments are missing.
- Most of the Figure annotation font sizes are way too small to be readable. This has to be adapted (Fig. 1a and d; Fig. 2; Fig. 3a,b,d; Fig. 4g).
- Some legends, e.g., Figure 1d, require more explanation.
- Factor 2 group, i.e., combination therapy, “explains no variance in the transcriptome,” which is surprising and needs to be discussed further.
- Some parts of the first two and last paragraphs of the discussion seem to be redundant and can be cut. Likewise, discussion paragraph 7, starting with “In this study, we used innovative graph-theoretical…” would probably fit better at the beginning.

Declarations

Potential competing interests: No potential competing interests to declare.