NEGATIVE SELECTION OF LIGAND-RECEPTOR INTERACTIONS MEDIATING LYMPHOCYTE INFILTRATION CONFER MELANOMA RESISTANCE TO IMMUNE CHECKPOINT BLOCKADE THERAPY BY TURNING HOT TUMORS TO COLD

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Background Immune checkpoint blockade (ICB) is a promising cancer therapy; however, response rates remain less than desired (less than ~40%) and resistance often develops.

Methods To learn more about ICB resistance mechanisms, we developed IRIS (Immunotherapy Resistance cell-cell Interaction Scanner), a machine learning method aimed at identifying candidate ligand-receptor interactions (LRI) that are likely to underlie ICB resistance in the tumor microenvironment (TME). Our approach considers two key components that such interactions should fulfill: they should be (1) differentially activated between the pre-treatment and post-treatment non-responder patients, and (2) they should be predictive of ICB response in pre-treatment patients.

Results We trained the model on the five largest publicly available melanoma bulk transcriptomics ICB cohorts and demonstrated its superior performance versus two states-of-the-art transcriptomics-based prediction methods (IMPRES and TIDE) in predicting ICB therapy response both in terms of RECIST criteria and patient survival. We further validated our identified resistance relevant LRIs in a melanoma single cell ICB cohort. Strikingly, LRIs highly activated in the pre-treatment group showed stronger predictive power for ICB response compared to the post-treatment non-responder group, which implies a potential negative selection of LRIs by tumors. Notably, many of these LRIs are mediating lymphocyte infiltration within the TME. Reassuringly, we further find a strong correlation between the activity of these LRIs and CD8+ T cells infiltration levels in the TME and are highly enriched in hot tumors in an independent cohort.

Conclusions Overall, these findings point to specific ligand-receptor interactions that mediate ICB resistance via inhibiting lymphocytes infiltration and turning hot tumors to cold ones.

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