PGE2-mediated NK cell reprogramming drives acquired immunotherapy resistance in lung adenocarcinoma

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INTRODUCTION

- Acquired resistance to PD-1 blockade poses a major challenge in lung adenocarcinoma, yet its underlying tumor-intrinsic mechanisms and immune remodeling dynamics remain unclear.
- The study aims to identify tumor-intrinsic drivers of acquired resistance using a longitudinally monitorable orthotopic mouse model and determine how these mediators impair antitumor immunity.

METHODS

- An orthotopic, bioluminescence-trackable LLC1 lung adenocarcinoma model in C57BL/6J mice was established to evaluate longitudinal responses to anti-PD-1 therapy.
- In vivo CRISPR/Cas9 loss-of-function screen was conducted to identify resistance drivers, followed by validation using TET-off inducible knockdown systems.
- RNA-seq, cAMP measurement, calcium flux assays, mouse/human NK-cell co-cultures, NK adoptive transfer, and selective EP2/EP4 antagonists or celecoxib were utilized to evaluate PGE2 signaling and NK-cell dysfunction.

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Figure 1. Establishment of a longitudinally monitorable in vivo model of acquired immunotherapy resistance.

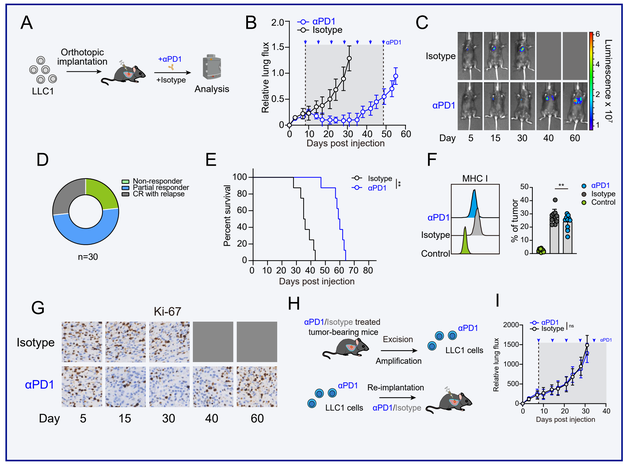


Figure 2. In vivo CRISPR screening identifies PGE2 as a key regulator of acquired resistance to immunotherapy.

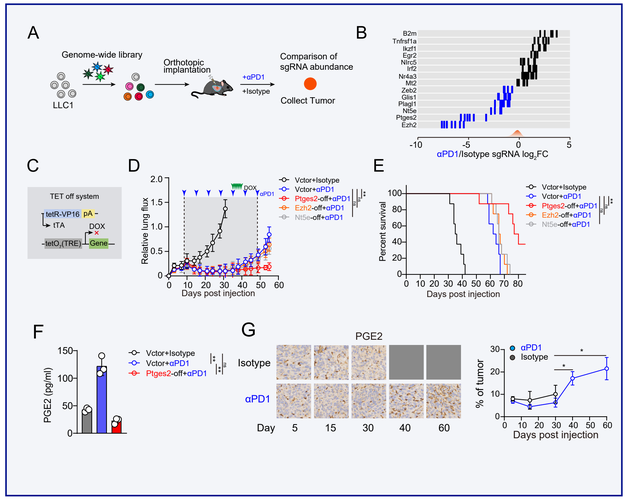


Figure 3. PGE2 mediates acquired resistance through NK cells.

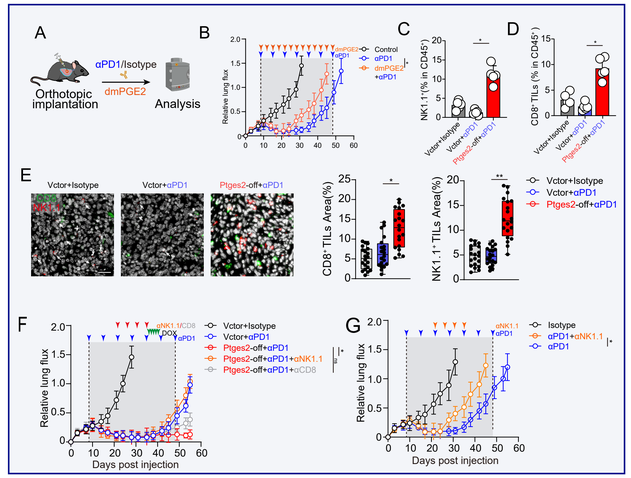


Figure 4. PGE2 derived from tumors with acquired resistance reprograms NK cells.

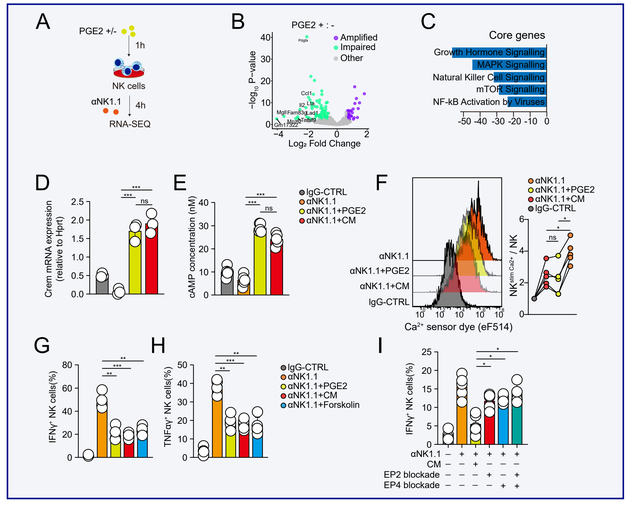
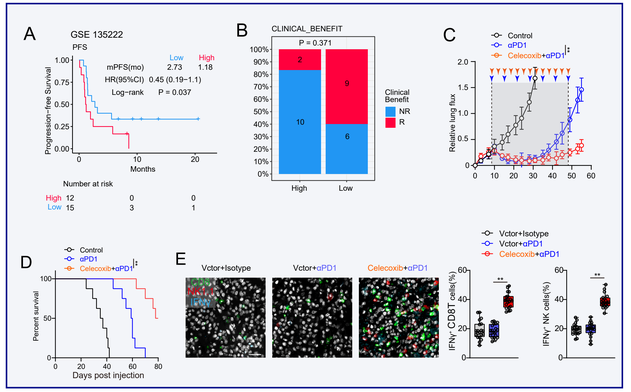


Figure 5. Pharmacologic blockade of PGE2 remodels the immune microenvironment and overcomes resistance to immunotherapy.



CONCLUSION

Targeting the COX-2/PGE2 axis effectively restores NK-cell-mediated immunosurveillance, presenting a viable, biomarker-guided translational strategy to overcome acquired immunotherapy resistance.

