



P2.040: Senescent Fibroblasts Promote Osimertinib Resistance in Lung Adenocarcinoma via Mitochondrial Transfer-Mediated Metabolic Reprogramming

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INTRODUCTION

- Drug-tolerant persister (DTP) cells represent a critical transitional state during the evolution of Osimertinib resistance in EGFR-mutant lung adenocarcinoma.
- Although senescence is a prominent feature of DTP cells, how the senescent stromal microenvironment supports their transition toward resistance remains unclear.
- We investigated the reciprocal interaction between fibroblasts and tumor cells during the DTP state and its role in resistance evolution.

DISCUSSION AND CONCLUSION

- Fibroblasts actively support DTP survival through mitochondrial donation during Osimertinib treatment.
- Mitochondrial transfer and subsequent fibroblast senescence form a reciprocal tumor–stroma circuit that promotes resistance evolution.
- Targeting this fibroblast–tumor metabolic interaction may provide an opportunity to eliminate DTP cells before stable resistance emerges.
- Further studies should define the molecular machinery governing mitochondrial transfer and identify druggable regulators of this process.

METHODS

- Osimertinib-induced DTP models were established in EGFR-mutant LUAD cells and characterized by transcriptomic and metabolic profiling.
- Co-culture and 3D tumor–stroma spheroid models were used to examine fibroblast–tumor interactions, mitochondrial transfer, and extracellular matrix remodeling.
- Live-cell imaging, Seahorse respirometry, proteomic analyses, and genetic interventions were used for mechanistic and functional validation.

REFERENCES & ACKNOWLEDGEMENTS

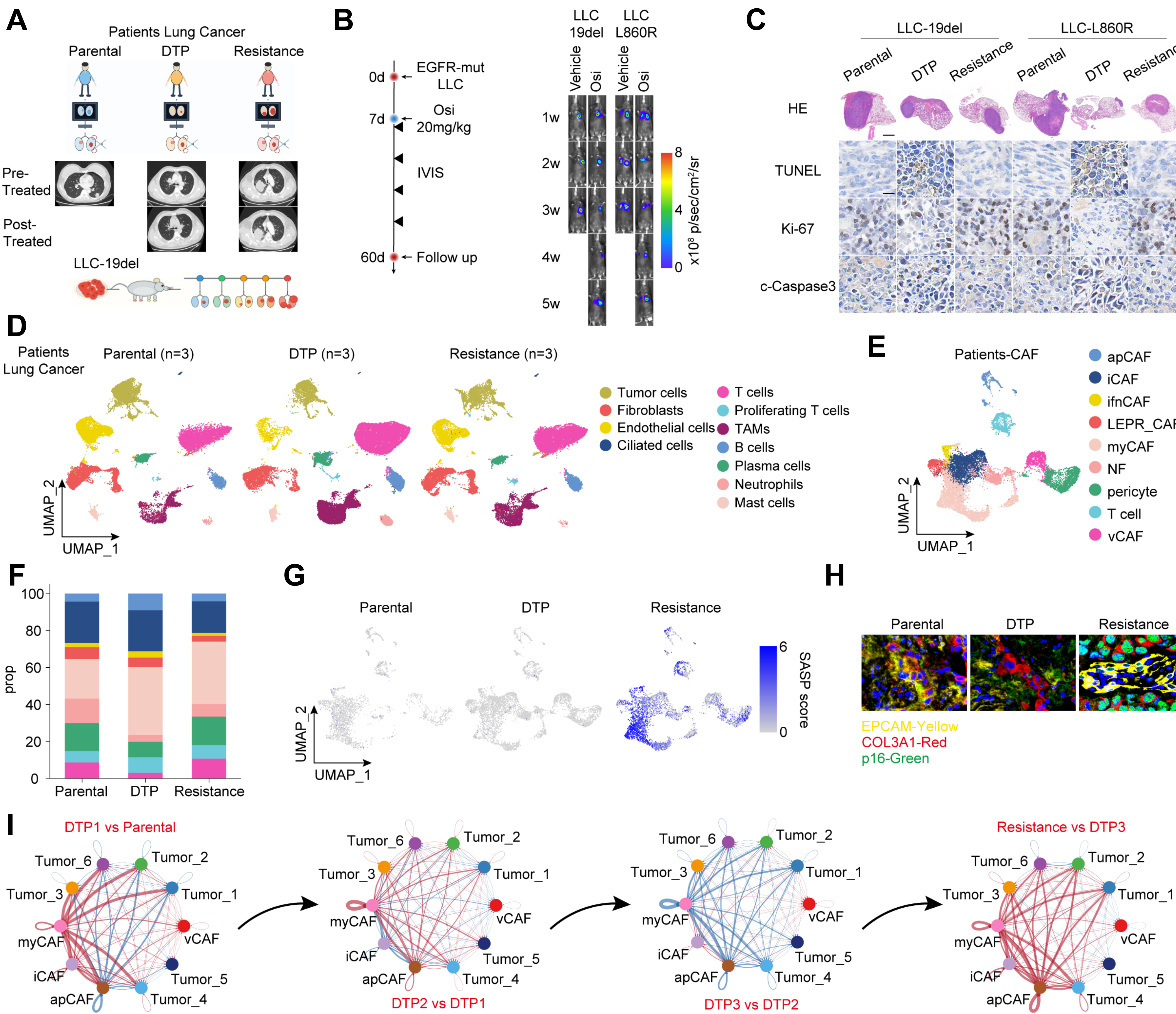
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RESULTS



- DTP cells displayed enhanced metabolic plasticity and increased OXPHOS during Osimertinib treatment.
- Fibroblasts transferred mitochondria to DTP cells to sustain bioenergetics, while subsequent fibroblast senescence generated an ECM-rich protective niche that facilitated resistance evolution.
- Blocking mitochondrial transfer or disrupting the senescent fibroblast-derived microenvironment delayed the emergence of Osimertinib resistance.