A032 · Single-Cell Transcriptomics Reveals a Transient Lipid-Associated Macrophage Response to Beta-Catenin/CBP Inhibition in Oral Squamous Cell Carcinoma

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Background: Aberrant Wnt/beta-catenin signaling promotes tumor progression in HPV-negative oral squamous cell carcinoma (OSCC), in part through interaction with the transcriptional coactivator CBP. We investigated how E7386, a small-molecule inhibitor of beta-catenin/CBP activity, affects the OSCC tumor microenvironment (TME).

Methods: We profiled ~71,000 cells from E7386- and vehicle-treated tumors in a syngeneic 4MOSC1 mouse model of tobacco-associated OSCC by single-cell RNA sequencing (n=4/arm). Treatment-associated compositional changes were assessed (sccomp), cell states characterized by annotation and gene set enrichment, and cell-cell communication inferred (CellChat). Findings were complemented by immunofluorescence (IF) and bulk RNA sequencing of E7386-treated 4MOSC1 cells in vitro.

Results: E7386 reduced tumor growth and increased epithelial cell death. Compositional analysis identified epithelial depletion (FDR=0.037) and selective expansion of two lipid-associated macrophage (LAM) populations (FDR=0.0015, 0.0044). LAM transcriptional signatures were enriched for lipid transport, endocytosis, and tissue remodeling. CellChat identified altered epithelial-LAM communication involving adhesion, lipid handling, and dying-cell recognition. IF revealed that LAMs accumulated near epithelial cell death early after treatment but diminished with continued treatment. Mouse bulk RNA sequencing identified suppression of proliferative and keratinization programs and induction of cellular stress and programmed cell death, showing significant transcriptional overlap with human OSCC cells treated with beta-catenin/CBP inhibitors.

Conclusion: E7386 induces coordinated tumor-intrinsic and TME responses, including a transient macrophage response consistent with the recognition and clearance of dying cells. These findings identify potential cellular and transcriptional features for evaluating the response to beta-catenin/CBP-targeted therapy in OSCC.