Researchers shed light on signaling pathway responsible for head and neck cancers

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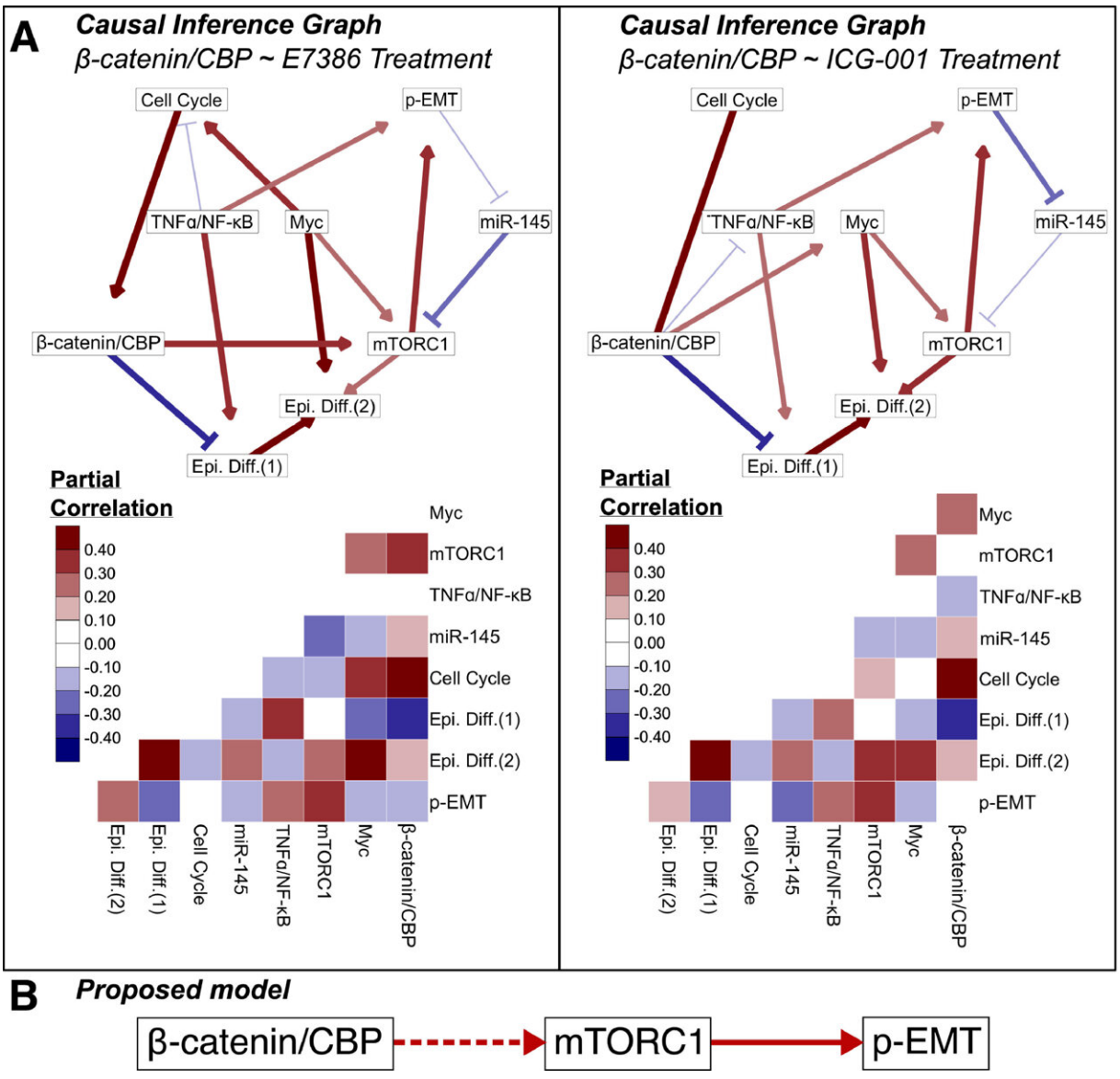

Causal Inference Models of Interactions Between Pathways/Cell States in Head

and Neck Cancer scRNAseq Data. A. Causal inference graphs indicated inferred causal relationships of pathways and cell states. The right and left graphs represent separate causal models including separate β-catenin/CBP gene sets, derived from either E7386 or ICG001 treatments, respectively. Partial correlation estimate maps are shown below each graph. The color scale for the vertices in the causal inference are in concordance with the partial correlation estimates. The full set of results for partial correlation and causal inference analysis are shown in Supplemental Table S3. B. Proposed causal model of mTORC1 activation by β−catenin/CBP upstream of induction p-EMT. The dashed line indicates that mTORC1 activation of β−catenin/CBP may be direct and/or mediated by Myc. Credit: *Translational Research* (2023). DOI: 10.1016/j.trsl.2023.05.007

Despite advances in defining the genomic characteristics of head and neck cancers, these malignancies continue to rank among the deadliest cancers with few targeted therapies available. An important challenge in designing effective treatments is intratumor heterogeneity, the presence of multiple subpopulations of cells with distinct genomic and molecular alterations, with some cells inherently more resistant to certain treatments.

A new study from researchers at Boston University Chobanian & Avedisian School of Medicine applied advanced bioinformatics and machine learning approaches to the analysis of large multi-omics head and neck cancer datasets and found activation of mTORC1 by b-catenin/CBP as an upstream driver of the malignancy-associated partial epithelial-mesenchymal transition (p-EMT) phenotype.

EMT is a biological process that plays a crucial role in embryonic development, tissue repairand various disease processes, including cancer. In cancer, EMT refers to the conversion of epithelial cells, which are typically found in the outer layers of organs and have strong cell-cell

adhesion, into mesenchymal cells, which are more migratory and invasive.

"This is of particular interest because both mTORC1 and b-cateninare important cancer hallmarks and p-EMT is a cellular process that is an early predictor of nodal metastasis, in which epithelial cells manifest characteristics of mesenchymal cells but do not fully undergo the complete transition," explained co-corresponding author Stefano Monti, Ph.D., associate professor of medicine at the School of Medicine.

According to the researchers, the study aimed to better characterize oral tumor heterogeneity including the aggressive cell subpopulations more likely to drive the early steps in cancer progression and invasiveness, with the ultimate goal of identifying candidate vulnerabilities that could be targeted therapeutically. "Understanding and addressing the diverse characteristics within tumors can help optimize therapeutic strategies, improve treatment outcomes and ultimately enhance patient survival rates," said Monti.

This collaborative multi-disciplinary study applied novel computational methods to the analysis of single cell data from primary oral cancer lesions. Findings were first validated in independent multi-omics datasets, including The Cancer Genome Atlas (TCGA) and the Cancer Cell Line Encyclopedia (CCLE), then further validated through functional molecular and pharmacologic perturbations using cell line-based experiments, as well as through pharmacologic perturbation experiments in experimental models.

The study's findings are of particularly timely significance, given the increasing evidence pointing to a crucial role of cells with a p-EMT phenotype in tumor progression to advanced disease and provide new information about additional therapeutic targets for this malignancy. In particular, the study's findings point to the potential of β-catenin/CBP

inhibition as a promising head and neck cancer treatment that distinctly targets more aggressive cells with elevated β catenin/CBP activity.

While this study's findings focus on head and neck cancer of the oral cavity, the researchers believe they are likely to be relevant to other cancer types, especially those that arise from mucosal tissues that line respiratory, gastrointestinal and genital tracts.

These findings appear online in the journal *Translational Research.*

More information: Eric R. Reed et al, β-catenin/CBP activation of mTORC1 signaling promotes partial epithelial-mesenchymal states in head and neck cancer, *Translational Research* (2023). DOI: 10.1016/j.trsl.2023.05.007

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