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Combinatorial Interventions Inhibit the Epithelial-to-Mesenchymal Transition and Support Hybrid Cellular Phenotypes[1] JORGE G. T. ZANUDO, S.N. STEINWAY, The Pennsylvania State University, P.J. MICHEL, D.J. FEITH, T.P. LOUGHRAN JR., University of Virginia School of Medicine, REKA ALBERT, The Pennsylvania State University — Epithelial-to-mesenchymal transition (EMT) is a developmental process hijacked by cancer cells to leave the primary tumor site and spread to other parts of the body. The molecular network regulating EMT involves the cooperation and cross-talk between multiple signaling pathways and key transcription factors, which we incorporated into systems-level logical network model for EMT. Using the EMT network model, we investigate potential EMT-suppressing interventions by identifying which individual and combinatorial perturbations suppress the induction of EMT by TGFβ, an important signal driving EMT in liver cancer. We find that all non-trivial interventions are combinatorial and involve the inhibition of the SMAD complex together with other targets, several of which we experimentally tested and validated using liver cancer cell lines. We compare the combinatorial interventions with the results from a network control method we recently developed, which allowed us to determine the specific feedback regulatory motifs through which the interventions suppress EMT. Our results also reveal that blocking certain network components gives rise to steady states that are intermediate to the epithelial and mesenchymal states, supporting the existence of hybrid epithelial-mesenchymal states.

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