

Abstract

Biological interactions among genes are essential for cellular signaling and regulatory processes, of which gene regulatory networks (GRNs) are an important component. GRNs coordinate transcriptional programs that govern cellular identity, differentiation, and adaptive responses. In cancer, disruption and large-scale rewiring of these regulatory circuits drive phenotypic plasticity, tumor progression, metastatic competence, and therapeutic resistance. While tumors at different clinical stages often display overlapping gene expression profiles, they exhibit marked differences in aggressiveness, metastatic potential, and therapeutic response. This suggests that alterations in regulatory topology and transcriptional control mechanisms, rather than expression change of transcription factor (TF) alone, might underlie disease progression. While gene expression changes across disease stages have been extensively characterized, how the underlying regulatory topology and TF dynamics evolve during cancer progression remains insufficiently understood.

In this study, we systematically decipher the topology and dynamics of GRNs driving cancer progression and therapy resistance. We first investigate stage-wise variations in network architecture by reconstructing cell type-specific GRNs using single-cell transcriptomic data from Lung adenocarcinoma (LUAD) patients and quantifying changes in connectivity and hub degree centrality. Our analyses reveal progressive restructuring of regulatory topology as tumors advance. We then examine regulatory dynamics to identify key TFs whose influence and activity shift across cancer stages in different cell types, highlighting candidate master regulators that orchestrate phenotypic transitions.

To further understand disease progression, we compare advanced-stage primary tumors with metastatic lesions to uncover regulatory adaptations associated with colonization of distant microenvironments. Metastatic samples exhibit distinct network configurations, indicating selective rewiring of core transcriptional circuits.

Extending the framework, we examine regulatory transitions from treatment-naïve (TN) tumors to therapy responders (R) and non-responders (NR) undergoing different treatment regimens, including immunotherapy combined with different groups of chemotherapy. Comparative network analyses reveal distinct patterns of regulatory remodeling associated with therapeutic outcome. In responders, we observed a dynamic and organized reconfiguration of gene networks that aligns with treatment efficacy. Conversely, non-responders exhibit stable regulatory states, suggesting that resistance programs are either pre-existing or become rapidly fixed upon treatment initiation, shielding the tumor from therapeutic pressure. Combination therapies further reshape network topology, indicating therapy-specific regulatory adaptations. Together, our findings establish cancer progression, metastasis, and therapeutic response as processes underpinned by coordinated changes in GRN topology and dynamics. This systems level framework highlights critical transcriptional regulators and network features that may serve as biomarkers and therapeutic targets in precision oncology.

Keywords: Gene regulatory network, topology, dynamics, cancer, metastasis, therapy response.