Uncovering the dynamic effects of DEX treatment on lung cancer by multiscale modeling of scRNA-seq and proteomics data

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Introduction

- Lung cancer remains the most common cause of cancer-related death[1]. Therefore, effective therapeutic strategies are in urgent need.
- Dexamethasone (DEX) has shown anti-cancer efficacy and anti-estrogenic activity in human non-small cell lung cancer (NSCLC)[2].
- We will integrate the knowledge and approaches from both Bioinformatics and Systems Biology domains to uncover the underlying molecular mechanisms of DEX therapy on lung cancer cells in this study.
- With the lung adenocarcinoma derived A549 cells after DEX treatment, we identified essential differentially expressed genes and their involved regulation pathways.
- We will develop a multiscale model to investigate the underlying mechanisms of anti-tumor drugs and examine the regulatory networks obtained by the above bioinformatical analysis.

Methods

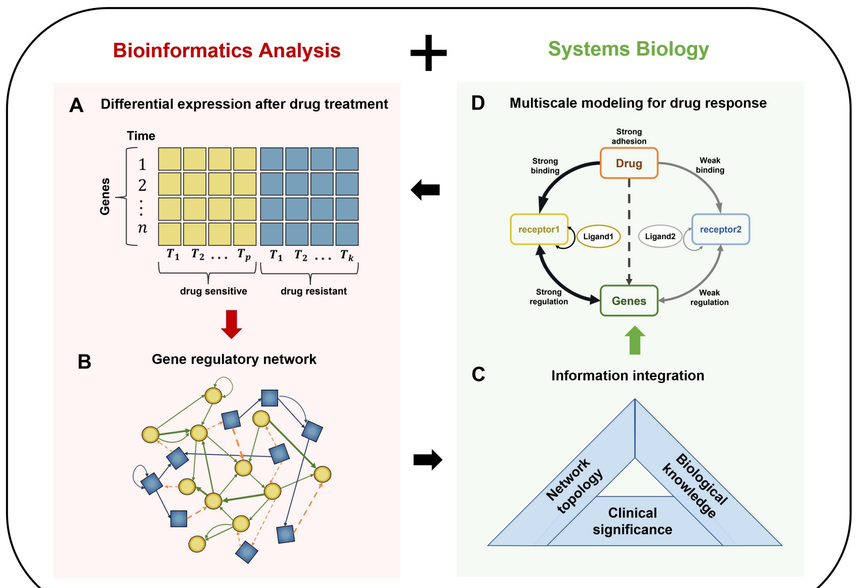

Figure 1. Schematic illustration of integrated Bioinformatics (anatomizing, reconstruction) and Systems Biology (integration, modeling) analysis on drug effect.

Bioinformatics methods

- Uniform manifold approximation and projection (UMAP)
- FindMarkers function[3]
- GENIE method[4]

Survival analysis

- Kaplan-Meier (KM) analysis
- Log-rank test

Pathway database

Gene sets derived from the Reactome pathway database

Enrichment test

- Enrichment test: clusterProfiler[5] package.
- Test P values: Benjamini-Hochberg correction

Mathematical modeling

Figure 1 was translated into a system of ordinary differential equations (ODEs)

Parameter optimization

Minimizing the residual error between empirical data and simulated results

Data availability

- The time-series scRNA-seq dataset of lung adenocarcinoma derived A549 cells: profiled using the sci-CAR protocol.
- The scRNA-seq can be downloaded from GEO with accession number GSM3271040.
- The protein data of SMAD2 and TGFβ1: derived from literature of Feng et al[6].

analyze the scRNA-seq data → **identify the variable genes and the involved interaction network** → **infer intracellular signaling pathways associated with clinical significance** → **built the mathematical model based on the signaling pathways**

Results

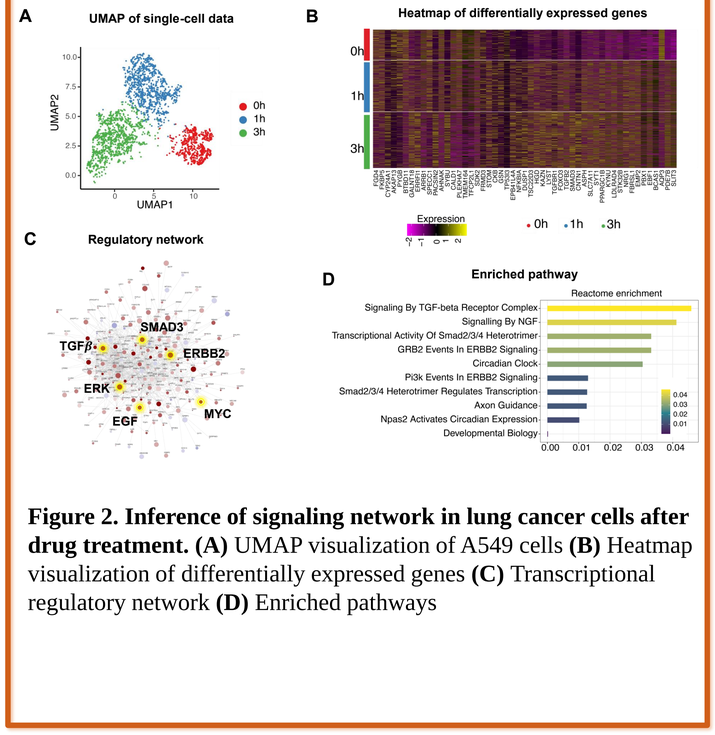

Figure 2. Inference of signaling network in lung cancer cells after drug treatment. (A) UMAP visualization of A549 cells **(B)** Heatmap visualization of differentially expressed genes **(C)** Transcriptional regulatory network **(D)** Enriched pathways

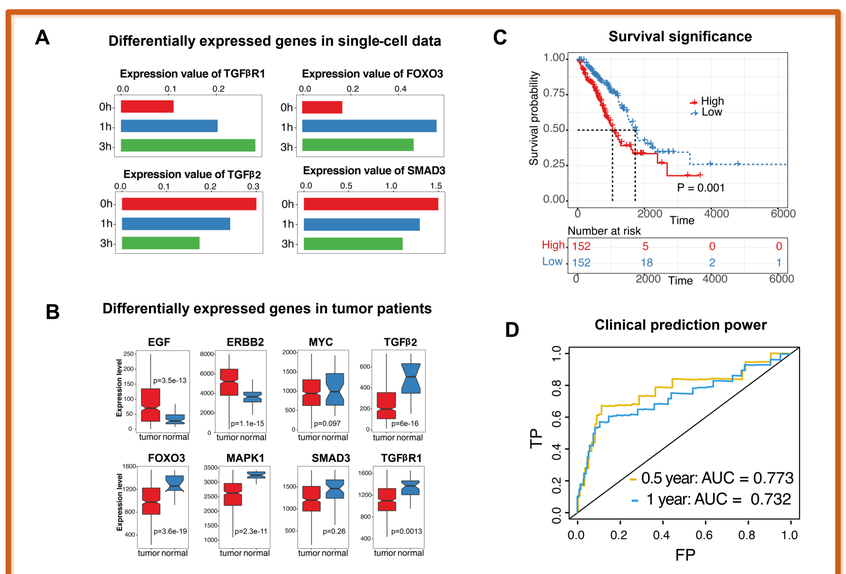

Figure 3. Clinical prognosis and significance of network hub genes.

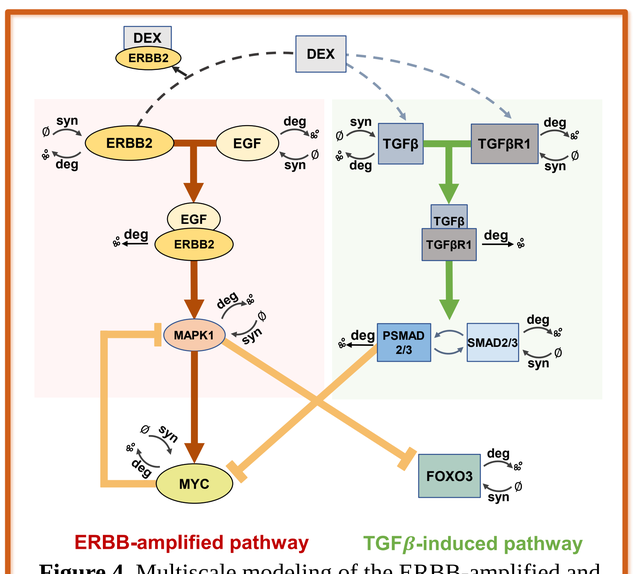

Figure 4. Multiscale modeling of the ERBB-amplified and TGFβ-induced feedback-crosstalk.

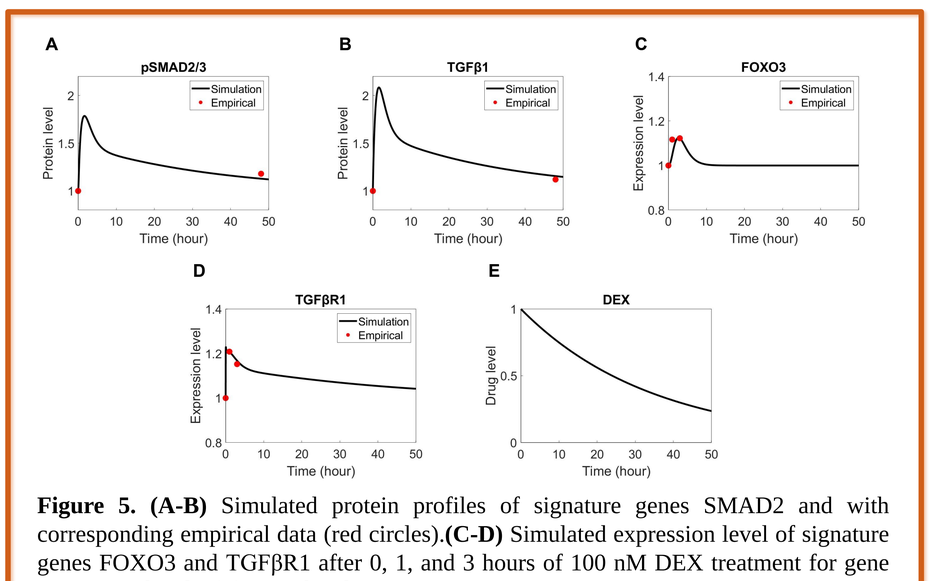

Figure 5. (A-B) Simulated protein profiles of signature genes SMAD2 and with corresponding empirical data (red circles).**(C-D)** Simulated expression level of signature genes FOXO3 and TGFβR1 after 0, 1, and 3 hours of 100 nM DEX treatment for gene expression levels. (E) DEX level over time.

Conclusion

- We provide an innovative and cross-disciplinary approach that could be further applied to immunotherapies and other cancer treatment.
- Our results convince the significance of scRNA-seq data identified genes.
- The model prediction provides insights into the potential effects of different DEX doses in cancer cells
- The insights can be applied to investigate the dynamics and effects of downstream regulators for tumorigenesis in future studies.

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