Uncovering the dynamic effects of DEX treatment on lung cancer by integrating bioinformatics inference and multiscale modeling

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***Short Abstract* — Lung cancer is one of the leading causes of cancer-related death. To better understand the underlying mechanisms affecting lung cancer therapeutics' implementation and effectiveness, we combine the power of Bioinformatics and Systems Biology to comprehensively uncover functional and signaling pathways of drug treatment using bioinformatics inference and multiscale modeling of both scRNA-seq data and proteomics data in this study. Key hub genes and their corresponding pathways are identified based on the lung adenocarcinoma derived A549 cells after DEX treatment. The study elaborates a multiscale model of tumor regulation to provide insights of computational studies in tumorigenesis and oncotherapy.**

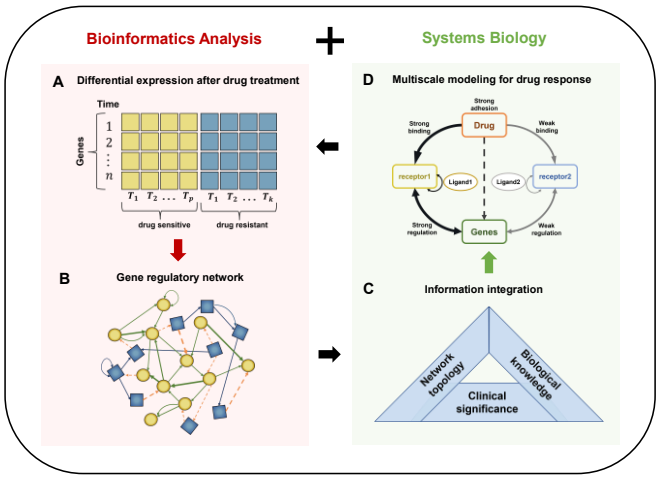
***Keywords* — Single-cell RNA-seq; multi-modal omics data; Bioinformatics inference; Multiscale modeling.**

I. PURPOSE

LUNG cancer remains the most common cause of cancer-related death, with over 1.8 million deaths expected globally in 2021 [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), whereby further study can be made to testify its efficacy. Single-cell RNA sequencing (scRNA-seq) allows for the interrogation of cellular hierarchies and the identification of cells transitioning between states [2-4]. In this study, 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.

II. METHODS AND RESULTS

Through the interrogation of regulatory network of those differentially expressed genes, we identified key hub genes including TGFβ, MYC, and SMAD3 varied underlie DEX treatment with the collected lung adenocarcinoma derived A549 cells after DEX treatment. Further enrichment analysis revealed the TGFβ signaling pathway as the top enriched term. Those genes involved in the TGFβ pathway and their crosstalk with the ERBB pathway presented a strong survival prognosis in clinical lung cancer samples. Moreover, we develop a multiscale model to investigate the underlying mechanisms of anti-tumor drugs and examine the regulatory networks obtained by the above bioinformatical analysis. A multiscale model of tumor regulation centered on both TGFβ-induced and ERBB-amplified signaling pathways was then developed to characterize the dynamic effects of DEX therapy on lung cancer cells. Our simulation results were well matched to available data of SMAD2, FOXO3, TGFβ1, and TGFβR1 over the time course. Moreover, we provided predictions of different doses to illustrate the trend and therapeutic potential of DEX treatment.



III. CONCLUSION

Our study provided an innovative and cross-disciplinary approach that could be further applied to immunotherapies and other cancer treatment. The comparison between experimental observation and mathematical modeling using both scRNA-seq data and proteomics data further convinces the significance of scRNA-seq data identified genes. Additionally, model prediction provides insights into the potential effects of different DEX doses in cancer cells, which can be applied to investigate the dynamics and effects of downstream regulators for tumorigenesis in future studies.

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